The gastrointestinal and biliary system

Gastrointestinal (GI) and liver disorders account for minor, everyday complaints as well as major health problems. Dietary measures can improve symptoms that are caused, for example, by poor eating habits, but, if these are not successful, phytomedicines are also useful. In fact, natural products are still the most commonly used remedies in cases of constipation, diarrhoea and flatulence. Plants and their derivatives also offer useful treatment alternatives for other problems such as irritable bowel syndrome, motion sickness and dyspepsia. In the case of some liver diseases, phytotherapy provides the only effective remedies currently available.

DIARRHOEA

Diarrhoea of sudden onset and short duration is very common, especially in children. It normally requires no detailed investigation or treatment, as long as the loss of electrolytes is kept under control. However, chronic serious cases of diarrhoea caused by more virulent pathogens are still a major health threat to the population of poor tropical and subtropical areas. The World Health Organization (WHO) has estimated that approximately 5 million deaths are due to diarrhoea annually (2.5 million in children under 5 years).

The first line treatment is oral rehydration therapy using sugar-salt solutions, often with added starch, and the use of gruel rich in polysaccharides (e.g. rice or barley 'water') is an effective measure. The polysaccharides of rice (*Oryza sativa*) grains are hydrolysed in the GI tract; the resulting sugars are absorbed because the co-transport of sugar and Na^+ from the GI lumen into the cells and mucosa is unaffected. Rice suspensions thus actively shift the balance of Na^+ towards the mucosal side, enhance the absorption of water and provide the body with energy, and the efficacy of rice starch has been demonstrated in several clinical studies. The treatment of diarrhoea in adults, particularly for travellers, may also include opiates or their derivatives, to reduce gastrointestinal motility. Many classical anti-diarrhoeal preparations contain opium extracts, or the isolated alkaloids morphine and codeine (e.g. kaolin and morphine mixture, codeine phosphate tablets), although these are controlled by law in some countries. Opioid derivatives such as loperamide, which have limited systemic absorption and, therefore, fewer central nervous system side effects, have superseded these agents to some extent but the natural substances are still used and are highly effective. Dietary fibre, including that found in bulk-forming laxatives (qv) can also be used to treat diarrhoea; in this case, the fibre is taken with only a small amount of water. There are other plant drugs which act in varying ways (for review see Palumbo 2006).

STARCH (AMYLUM) EU

Starch is used for rehydration purposes and may be derived from rice (*Oryza sativa* L.), maize (*Zea mays* L.) or potato (*Solanum tuberosum* L.). Giving starch-based foods (like gruels) has been shown to be therapeutically beneficial and is a first line treatment in minor self-limiting cases. These are also used as excipients for tablet production. Starch particles give a very characteristic microscopic

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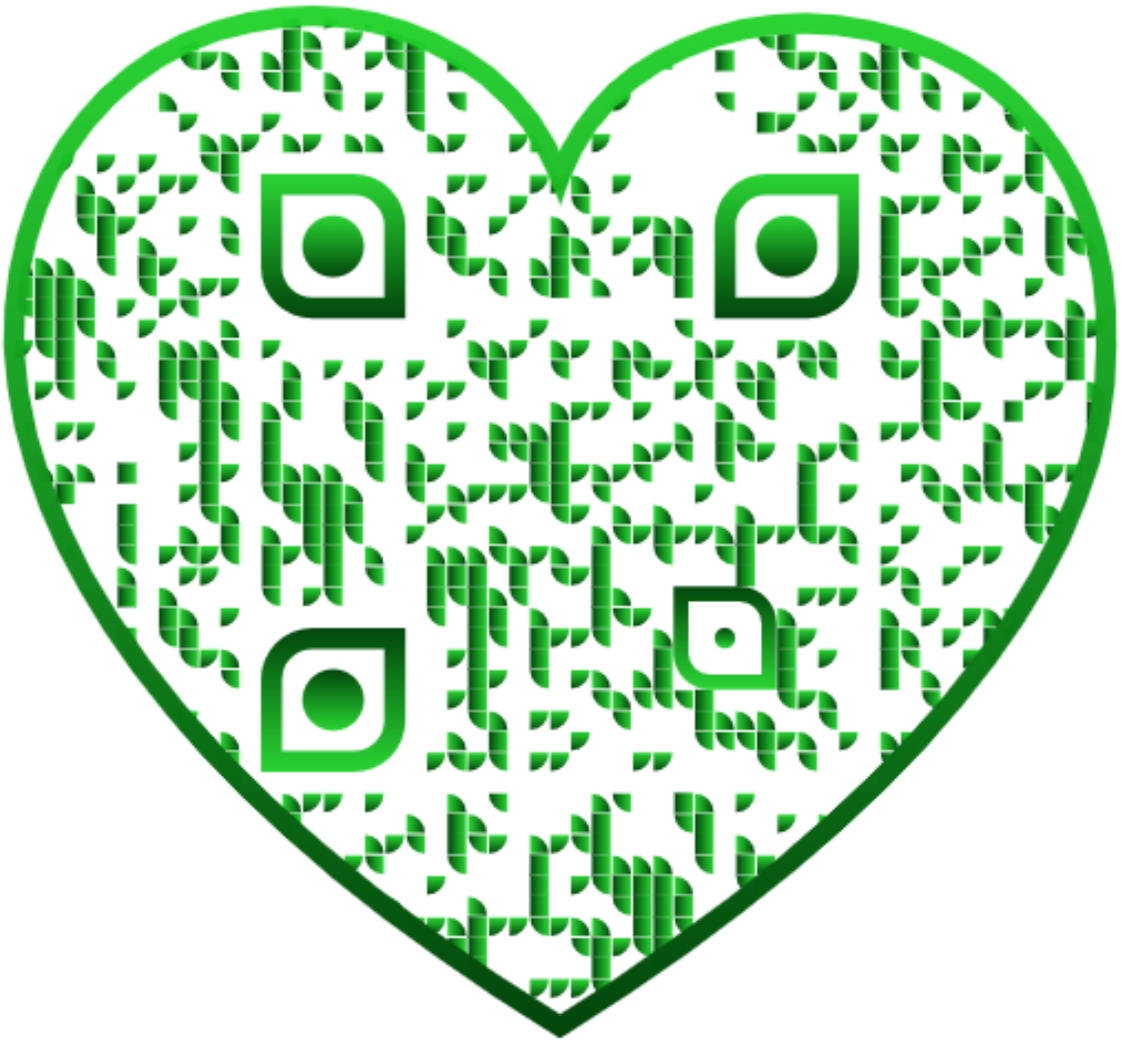


picture, which can be used to differentiate the various types, but chemical analysis is rarely carried out.

TANNIN-CONTAINING DRUGS

Tannins are astringent, polymeric polyphenols, and are found widely in plant drugs. The most important herbs used in the treatment of diarrhoea include Greater Burnet, *Sangisorba officinalis* L., Black Catechu, *Acacia catechu* Willd., Oak bark, *Quercus robur* L., Tormentil, *Potentilla erecta* (L.) Rausch., and even tea and coffee; however, many others are used in different countries (Palumbo 2006). Tannin-containing drugs are generally safe, but care should be taken with concurrent administration of other drugs since tannins are not compatible with alkalis or alkaloids, and form complexes with proteins and amino acids.

CONSTIPATION

Constipation is often due to an inappropriate diet and lack of physical activity, for example while being confined to bed during illness, or the result of taking other medication (especially opioids). It is characterized by reduced and difficult bowel movements, and is said to be present when the frequency of bowel movements is less than once in 2 or 3 days. Although the causes are not usually serious in nature, continuous irregularity in bowel movements should be investigated in case there is a risk of malignant disease. The subjective symptoms (straining heavily, hard stools, painful defecation and a feeling of insufficient evacuation) make it one of the most commonly reported health problems. Constipation is often associated with other forms of discomfort such as abdominal cramps, dyspepsia, bloating and flatulence. Alternating diarrhoea and constipation is a symptom of irritable bowel syndrome.

Various types of plant-derived laxative are used: stimulant laxatives (purgatives), which act directly on the mucosa of the GI tract; bulk-forming laxatives, which act mainly via physicochemical effects within the bowel lumen; and osmotic laxatives, which act by drawing water into the gut and thus softening the stool. Osmotic laxatives may be mineral in origin, for example magnesium salts, or derived from natural products such as milk sugars.

Patients generally require rapid relief from constipation, and the immediate effect of stimulant and saline purgatives is very well known. Although there is no problem using them occasionally, or on a short-term basis (less than 2 weeks), or prior to medical intervention such as X-ray (Roentgen) diagnostics, long-term use should be discouraged. The exception is for patients taking opioids for pain management, who may need to use stimulant laxatives routinely. The most important adverse effect of the long-term use of the stimulant laxatives and saline purgatives is electrolyte loss. Hypokalaemia, pathologically reduced levels of potassium (K^+), may even worsen constipation and cause damage to the renal tubules. The risk of hypokalaemia is increased with administration of some diuretics and hypokalaemia exacerbates the toxicity of the cardiac glycosides (e.g. digoxin), which are often prescribed for elderly patients. Hyperaldosteronism, an excess of aldosterone production, which leads to sodium (Na^+) retention, and again to potassium loss and hypertension, is also a risk. In general, the use of bulk-forming or osmotic laxatives is preferred, unless there are pressing reasons for using a stimulant laxative.

BULK-FORMING LAXATIVES

These are bulking agents with a high percentage of fibre and are often rich in polysaccharides, which swell in the GI tract. They influence the composition of food material in the GI tract, especially via the colonic bacteria, which are thus provided with nutrients for proliferation. This in turn influences the composition of the GI flora and the metabolism of the food in the tract (including an increase in gas, or flatus). Fibre-rich food is part of a healthy diet, but processed food and modern life styles have generally reduced fibre intake. Bulk-forming laxatives are generally not digested or absorbed in the GI tract, but pass through it largely unchanged.

Bulking agents can be distinguished from swelling agents in that bulking material contains large amounts of fibre, whereas swelling material is generally composed of plant material (seeds) with a dense cover of polysaccharides on the outside. Both types of medicinal drugs may swell to a certain degree by the uptake of water, but swelling agents in the strict sense include only medicinal plants that form mucilage or gel. The **swelling factor** (which compares the volume of drug prior to and after soaking it in water) is an indicator of the amount of polysaccharides present in the drug and is generally used as a marker for the quality of bulk-forming laxatives. The European

Table 14.1 Swelling factors of various bulk-forming laxatives

COMMON NAME	BOTANICAL SOURCE	SWELLING FACTOR (EUR. PH.)	NOTES
Ispaghula seed	*Plantago ovata*	≥9 (seed) ≥40 (testa of the seed)	
Psyllium seed	*Plantago psyllium* and *P. arenaria*	≥10	
Linseed	*Linum usitatissimum*	≥4 (entire seed) ≥4.5 (ground seed)	Also rich in fatty acids (in endosperm of seed)
Wheat bran	*Triticum aestivum*	–	Rich in fibre

Pharmacopoeia requires a minimal value of the swelling factor for each agent, and the swelling factors of the phytomedicines detailed below are shown in Table 14.1. Preparations of bulk-forming laxatives are always taken with plenty of water. They can, paradoxically, be used to treat diarrhoea if given with very little fluid; they then absorb the fluid from the lumen and increase the consistency of the stool.

LINSEED (FLAX), *LINUM USITATISSIMUM* L. (LINI SEMEN) EU

Linseeds are the ripe, dried seeds of flax (*Linum usitatissimum*, Linaceae), a plant grown for its fibre (used in the clothing industry) and for the seed oil, which is used in paints and varnishes, and to make oil cloth ('linoleum'). Flax, with its characteristic blue flowers, is an annual, and has long been under human cultivation. The dark brown (less often yellowish-white) seeds are oblong or ovate with a characteristically pointed end. They are tasteless but slowly produce a mucilaginous feel when placed in the mouth. The outer layer of the seed (testa) is rich in polysaccharides, while the inner part of the seed, which contains the endosperm and the cotyledons, is rich in fatty oil. If the seeds are taken whole, the inner layer of the testa is only partially digested in the GI tract and they will be excreted in the entire form, and the fatty acids will not be released. The swelling factor should at least be 4 (entire seeds) or 4.5 (powdered drug). Linseed also possesses cholesterol-lowering properties, and contains phytoestrogenic lignans.

PLANTAGO SPECIES

Ispaghula, *Plantago ovata* Forssk. (Plantaginis ovatae semen) EU

The dark brown, glossy seeds from *Plantago ovata* (Indian fleawort, blond psyllium, Plantaginaceae) are useful in the treatment of chronic constipation. They are broadly elliptical in shape, up to 3.5 mm long, and are practically tasteless, becoming mucilaginous when chewed. They can help to maintain or achieve a regular bowel movement and are also useful in irritable bowel syndrome. The swelling factor should be >9 for the entire seeds and >40 for the seed husk, which is the most widely used part. The usage is similar to that of psyllium (fleawort, below).

Psyllium, *Plantago psyllium* L. and *P. arenaria* L. (Psyllii semen) EU

The brown, shiny, elliptical to ovate seeds (2–3 mm long) are obtained from two species of the plantain family (Plantaginaceae). *Plantago psyllium* (=*Plantago afra* L., fleawort, black or dark psyllium, plantain) and *P arenaria* (=*P indica*, fleawort, plantain) yield useful and commonly used emollients and bulk laxatives which help in maintaining a regular bowel movement. The seeds are narrower and somewhat smaller than ispaghula seeds. An essential characteristic of high-quality material is a high swelling factor.

Wheat bran, *Triticum aestivum* L.

Bran is less useful as a laxative (except when taken as a natural part of the diet, e.g. in breakfast cereal), since it contains phytic acid, which in high concentrations can complex with and, therefore, reduce the bioavailability of vitamins and minerals taken at the same time. However, in some patients, wheat bran (the husk from the grains of *Triticum aestivum*) is more effective than other swelling agents, and preparations containing it are available for prescribing. These are taken in water.

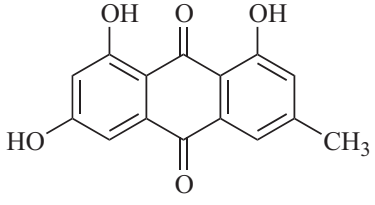
OSMOTIC LAXATIVES

Osmotic laxatives, such as lactulose or lactose, which are dimeric sugars derived from milk, are a useful and widely used approach to the treatment of long-term constipation. Lactose is split in the GI tract into glucose and galactose, and galactose is not generally resorbed well. Consequently, the bacteria of the colon

metabolize this sugar. The resulting acids, including lactic acid and acetic acid, have an osmotic effect, and the bacteria in the colon multiply more rapidly. This results in softening and increasing in the amount of faeces, with a subsequent increase in GI peristalsis.

STIMULANT LAXATIVES

Stimulant laxatives are derived from a variety of unrelated plant species, which only have in common the fact that they contain similar chemical constituents. These are anthraquinones such as emodin (Fig. 14.1) and aloe-emodin, and related anthrones and anthranols. Anthraquinones are commonly found as glycosides in the living plant. Several groups are distinguished, based on the degree of oxidation of the nucleus and whether one or two units make up the core of the molecule. The anthrones are less oxygenated than the anthraquinones and the dianthrones are formed from two anthrone units (Fig. 14.2). Studies using dianthrone glycosides such as sennosides A and B suggest that most of these compounds pass through the upper GI tract without any change; however, they are subsequently metabolized to rhein anthrone in the colon and caecum by the natural flora (mainly bacteria) of the GI tract. Anthranoid drugs act directly on the intestinal mucosa, influencing several pharmacological targets, and the laxative effect is due to increased peristalsis of the colon, reducing transit time and, consequently, the re-absorption of water from the colon. Additionally, the stimulation of active chloride secretion results in an inversion of normal physiological conditions and a subsequent increased excretion of water. Overall, this results in an increase of the faecal volume with an increase in the GI pressure. These actions are based on the well-understood effects of chemically defined constituents; consequently, phytomedicines containing them are usually standardized to specified anthranoid content (see Chapter 9).

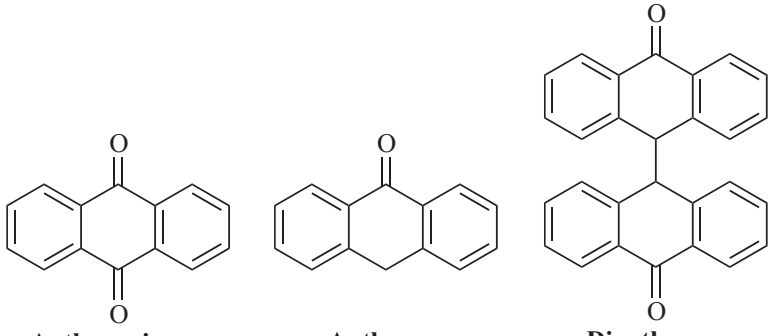


Emodin

Fig. 14.1

TOXICITY OF ANTHRANOID DRUGS

The monomeric aglycones (especially emodin and aloe-emodin) have been shown to have genotoxic and mutagenic effects using bacterial and *in vitro* systems such as the Ames test, and in mammalian cell lines. The long-term use of anthranoids may result in a (reversible) blackening of the colon (*Pseudomelanosis coli*), which is due to the incorporation of metabolites of the anthranoids and is thought to be associated with an increased risk of colon carcinoma. In practice, few toxic effects have been described, apart from those involving electrolyte loss described above. More immediate effects of anthranoid-containing drugs are colic and griping pains due to increased spastic contractions of the smooth musculature of the GI tract. Aloes and senna leaves are particularly prone to produce these. A synthetic derivative, danthrone (also known as dantron; not to be confused with the naturally occurring dianthrone), has been developed and, although effective, it is used only in palliative care due to its carcinogenic potential.



Anthraquinone **Anthrone** **Dianthrone**

Fig. 14.2

FRANGULA, *RHAMNUS FRANGULA* L. (FRANGULAE CORTEX); BUCKTHORN, *R. CATHARTICA* L. (RHAMNI CATHARTICI CORTEX) AND CASCARA, *R. PURSHIANA* DC. (RHAMNI PURSHIANI CORTEX) EU

The barks of several species of Rhamnaceae are used for their strong purgative effects. *Rhamnus frangula* (glossy buckthorn, frangula) has a milder action than *R. cathartica* (European buckthorn) and the berries are used in veterinary medicine. (The fruit also yields a dye, the colour of which depends partly on the ripeness.) The bark of *R. purshiana* (American buckthorn, known in commerce as Cascara sagrada) is the other main species used medicinally.

R. frangula is a densely foliated, thornless bush or tree, reaching a height of 1–7 m, common in damp environments such as bogs and along streams in North and Central Europe, as well as northern Asia. The cut bark is grey-brown with numerous visible grey-white lenticels. The leaves are broadly elliptical to obovate, about 3.5–5 cm long. The black, pea-sized berries develop from small greenish-white flowers.

Buckthorn (*R. cathartica*) is a thorny shrub with toothed leaves and a reddish brown bark; the berries are black and globular.

Cascara (*R. purshiana*) is native to the Pacific coast of North America but grows widely elsewhere. It is found in commerce in quilled pieces, often with epiphytes (lichen and moss) attached.

Constituents

***R. frangula*.** Glucofrangulin A (Fig. 14.3) and B, which are diglucosides differing only in the **type of sugar at C6.**

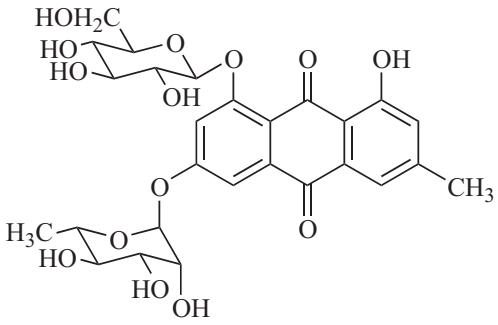
***R. cathartica*.** Emodin, aloe-emodin, chrysophanol and rhein glycosides, frangula-emodin, rhamnicoside, alaterin and physcion.

***R. purshiana*.** Cascarosides A (Fig. 14.3), B, C, D, E and F (which are stereoisomers of aloin and derivatives), with minor glycosides including barbaloin, frangulin, chrysaloin, palmidin A, B and C and the free aglycones.

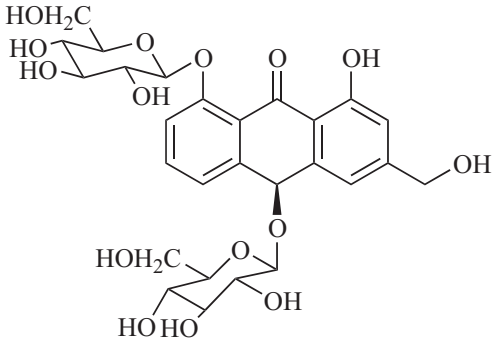
The anthrone and dianthrone glycosides, which are present in the fresh bark of these species, have emetic effects and may result in colic. In order to oxidize these compounds to anthraquinones with fewer undesirable side effects, the drug has either to be kept for a year or it is 'aged artificially' by heating it for several hours to 80–100°C.

SENNA, *CASSIA SENNA* L. AND *C. ANGUSTIFOLIA* VAHL (SENNA) (SENNAE FRUCTUS, SENNAE FOLIUM) EU

The genus *Cassia* (Caesalpiniaceae) is very large, with about 550 species, mostly occurring in warm temperate and tropical climates. The species are not native to Europe and were an important drug of early trading; the name 'Senna' is of Arabic origin and was recorded as early as the 12th century. Two shrubs from the genus *Cassia* (formerly called *Senna*) yield the drugs senna leaves and senna fruit: *Cassia senna* L. (syn. *C. acutifolia* L., Alexandrian senna) and *C. angustifolia* Vahl (Tinnevelly senna). The common names were derived from their original trade sources and are only applied to the fruits (pods). The second species is considered to be the milder in activity. Both the leaves and the fruits have typical microscopic characteristics, including the highly diagnostic, single-celled warty trichomes and the



Glucofrangulin A



Cascaroside A

Fig. 14.3

crystal sheath of calcium oxalate prisms around the fibres, but it is possible to distinguish the two species microscopically.

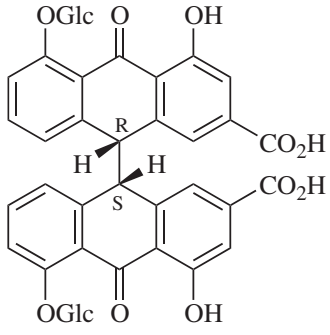
Constituents

Leaf. Sennosides A and B (Fig. 14.4), which are based on the aglycones sennidin A and sennidin B; sennosides C and D, which are glycosides of heterodianthrones of aloe-emodin and rhein; palmidin A, rhein anthrone and aloe-emodin glycosides and some free anthraquinones. *C. senna* usually contains greater amounts of the sennosides.

Fruit. Sennosides A and B and a related glycoside sennoside A1. The sennosides, which are dianthrones, differ in their stereochemistry at C_{10} and $C_{10'}$, as well as in their substitution pattern. *C. senna* usually contains greater amounts of the sennosides.

The structure of sennoside B is given in fig. 14.4. The Eur. Ph. standard is for a glycoside content of not less than 2.5% for the leaf, 3.5% for *C. senna* fruit and 2.2% for *C. angustifolia* fruit, calculated as sennoside B. Other secondary metabolites such as flavonoids, tannins and bitter compounds are also present but not defined in the standard. The way in which the plant material is dried has a strong influence on the amount of glycosides and accordingly on the quality of the product (see above).

The other main botanical anthranoid drugs are aloes *Aloe vera, A. barbadensis* and other species) and rhubarb (*Rheum raponticum* and others). These are used to a lesser extent nowadays.



Sennoside B

Fig. 14.4

INFLAMMATORY GI CONDITIONS: GASTRITIS AND ULCERS

Inflammation of the gastric mucosa, or gastritis, is an acute inflammatory infiltration of the superficial gastric mucosa, predominantly by neutrophils. It is generally treated with antacids (magnesium and aluminium salts) and emollients (alginate, mucilages), but other phytomedicines are still occasionally used (e.g. chamomile and liquorice). These agents, especially liquorice, were used to treat gastritis and ulceration until superseded by the synthetic H_2-receptor-blocking agents (cimetidine, ranitidine, etc. and proton pump inhibitors (omeprazole, lansoprazole). Now that infection with *Helicobacter pylori* is known to be a causal factor in ulceration, antibiotic therapy is the first-line treatment of choice. Most pharmaceuticals for mild gastric inflammation contain a mixture of an emollient, to line and soothe the mucosa (e.g. an agar suspension), an antacid and possibly a carminative such as peppermint or anise oil (see section on dyspepsia).

ALGINATE EU

Alginate, or alginic acid, is an anionic polysaccharide distributed widely in the cell walls of brown algae including *Laminaria*, and *Ascophyllum nodosum*. Raw or dried sea weed is washed with acid to remove cross-linking ions that cause the alginate to be insoluble. It is then dissolved in alkali, typically sodium hydroxide, to produce a viscous solution of alginate. The solution is filtered to remove the cell wall debris and leave a clear alginate solution. Alginate binds with water to form a viscous gum and acts as a protective coating over the walls of the stomach and oesophagus.

CHAMOMILE *MATRICARIA RECUTITA* L. (MATRICARIAE FLOS) EU

German (syn. Hungarian) chamomile flowers are derived from *Matricaria recutita* (syn. *Chamomilla recutita, Matricaria chamomilla*, Asteraceae, the daisy family). They have a pleasant aromatic odour. The flower heads have a diameter of approximately 10 mm and are composed of many minute flowers (called florets) which are either tongue-shaped ('ligulate florets', found at the margin) or tubular ('disk' florets, found in the disk-like centre). True chamomile has a hollow receptacle (the part of the stalk where the flower parts are attached)

and is devoid of the small leaf-like structures (stipules) that are common with the non-medicinal members of this genus. Chamomile is grown on a large scale, especially in Eastern Europe, Spain, Turkey, Egypt and Argentina, and has been known as a medicinal plant for several thousands of years. It is used internally for spasmodic and inflammatory illnesses of the GI tract.

Constituents

The flower heads are rich in essential oil. Two types of essential oil are recognized: one rich in bisabolol (levomenol) (Fig. 14.5) and the other in bisabolol oxides. Both contain other terpenoid compounds, including guaianolides such as matricin which are only found in the crude drug. The characteristic, dark blue azulenes (e.g. chamazulene; Fig. 14.5) are produced during steam distillation and only found in the essential oil. Flavonoids (up to 6%), especially apigenin and apigenin-7*O*-glycoside, caffeic acid derivatives and spiro ethers are also present. The components of the essential oil levomenol (α-bisabolol), its oxides, chamazulene, some unusual spiro ethers and the flavonoids (especially apigenin) are all essential for the pharmacological effects of the drug. The minimum amount of essential oil required by the Eur. Ph. is 0.4%.

Therapeutic uses and available evidence

Anti-inflammatory, spasmolytic, antibacterial and antifungal effects are well established both pharmacologically and clinically (see McKay and Blumberg 2006a). Chamomile is relatively safe, although allergic reactions can occur as with all plants of the family Asteraceae.

Note. The flower heads of *Chamaemelum nobile* (L.) All. (syn. *Anthemis nobilis* L., English chamomile, Roman chamomile) have a pharmacological profile similar to that of *Matricaria recutita*, and are included in the Eur. Ph. However, there is much less scientific and clinical evidence to support their use than for *M. recutita*.

LIQUORICE, *GLYCYRRHIZA GLABRA* L. (LIQUIRITIAE RADIX) EU

Liquorice (licorice) root is derived from the inner part of the root and underground stem (rhizome) of *Glycyrrhiza glabra* (Fabaceae, the bean family). The peeled drug is of much higher quality than the root with the bark, and is produced in several south-eastern European countries, Turkey, China and Russia. It has a very characteristic taste and smell, and is used in confectionery. The sweet taste also makes the identification of the drug relatively easy and so adulteration is uncommon. Microscopic identification is possible and uses characteristic crystals of oxalate, especially in the form of a sheath of parenchyma surrounding the phloem fibres, as well as the structure of the parenchyma. Liquorice is used to relieve gastric inflammation, specifically in the case of peptic ulcers and duodenal ulcers, but its use as a GI remedy is controversial because of its mineralocorticoid action. The dose should not exceed 200–600 mg of glycyrrhizin daily and the duration of treatment should be at most 4–6 weeks. More potent synthetic pharmaceuticals are now available, and it is now rarely used for this purpose. Liquorice and its preparations are contraindicated in cholestatic liver disorders, liver cirrhosis, hypertension, hypokalaemia, severe renal failure and pregnancy. With excessive use, liquorice-containing confectionery may result in similar undesired side effects. Liquorice is also used in respiratory complaints as an expectorant, mucolytic and antitussive agent.

Constituents

The most important bioactive secondary metabolite is glycyrrhizic acid (also known as glycyrrhizin; Fig. 14.6), a water-soluble pentacyclic triterpene

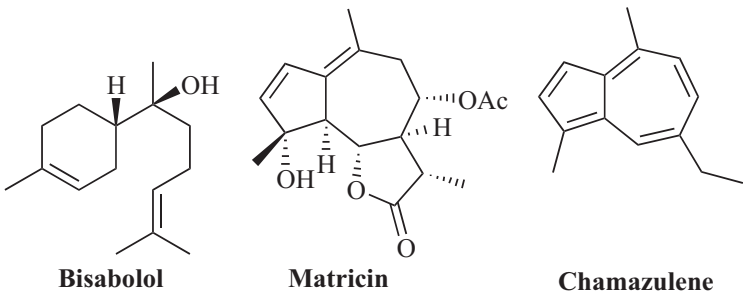


Fig. 14.5

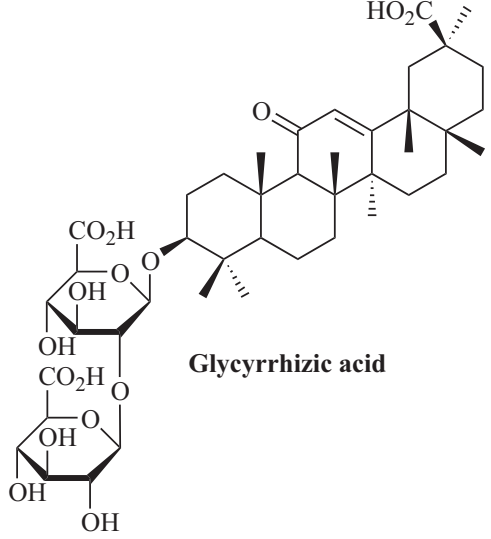


Fig. 14.6

saponin which gives the drug its characteristic sweet taste (it is about 50 times sweeter than sucrose). The genin (glycyrrhetinic acid or glycyrrhetin), on the other hand, is not sweet but very bitter. Liquorice also contains numerous flavonoids (chalcones and isoflavonoids), coumarins and polysaccharides, which contribute to the activity.

DYSPEPSIA AND BILIOUSNESS

Dyspepsia and 'biliousness' are closely associated with eating habits and are very common complaints. Patients describe the symptoms as nausea, pain and cramps, distension, heartburn and the 'inability to digest food', often experienced after rich meals. The condition is treated either with cholagogues or with bitter stimulants. A cholagogue is an agent that stimulates bile production in the liver, or promotes emptying of the gallbladder and bile ducts. Although clinical evidence is largely lacking, plant-based cholagogues are frequently prescribed by family doctors in Germany based on observational evidence and a long tradition of use, but they should not be used in cases of bile duct obstruction or cholestatic jaundice.

Liver disease is not treated as such by conventional medicine, but herbal medicine has a number of clinically proven treatments which help to protect the liver from damage and reverse some of the indicators of liver malfunction. The most important of these is silymarin, but other herbs are widely used for liver disease, although mainly with much less clinical evidence in support.

Phytomedicines used as bitter stimulants, such as Gentian and Wormwood, act directly on the mucosa of the upper part of the GI tract and especially of the bitter receptors on the tongue, stimulating the secretion of saliva and gastric juices and influencing the secretion of gastrin. An aperitif containing 'bitters', taken about half an hour before eating, stimulates gastric and biliary secretion; however, it is not known whether these effects are restricted to patients with a reduced secretory reflex, or whether an increase also occurs in healthy people.

ARTICHOKE, *CYNARA SCOLYMUS* L. (CYNARAE FOLIUM) EU

This well-known member of the Asteraceae yields the globe artichoke (a food common in French cuisine), which is the large flower head of the plant. The medicinal part is the leaf, which is used to treat indigestion and dyspepsia, and to lower cholesterol levels.

Constituents

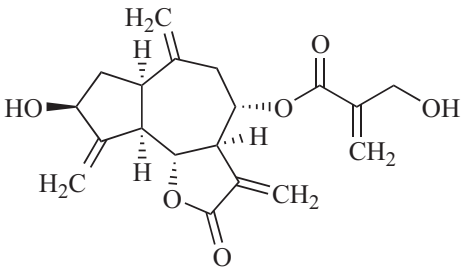
The leaf contains the bitter sesquiterpene lactone cynaropicrin, several flavonoids and derivatives of caffeoylquinic acid, including cynarin (Fig. 14.7).

Therapeutic uses and available evidence

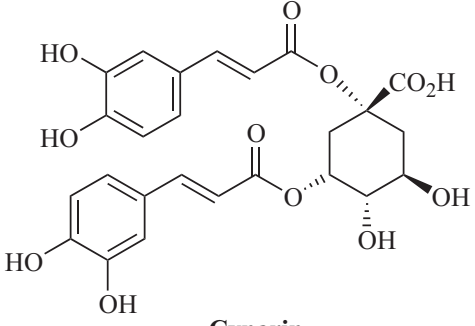
Antihepatotoxic effects, cholagogue activity and a reduction of cholesterol and triglyceride levels have been reported, and are now known to be due to inhibition of cholesterol biosynthesis. Clinical studies have shown that artichoke leaf extract can improve parameters such as fat intolerance, bloating, flatulence, constipation, abdominal pain and vomiting, and increase bile flow, at a daily mean dose of 1500 mg. For further details, see Bundy et al 2008, and Wider et al 2009. Artichoke extract is also useful in irritable bowel syndrome (Walker et al 2001).

GENTIAN, *GENTIANA LUTEA* L. (GENTIANAE RADIX) EU

The yellow gentian (*G. lutea*, Gentianaceae) is, after ethanol, the most important ingredient of the Alpine beverage *Enzianschnaps*, used as a digestive stimulant, taken after a large meal. Most medicinal products are made using the rapidly dried and non-fermented drug.



Cynaropicrin



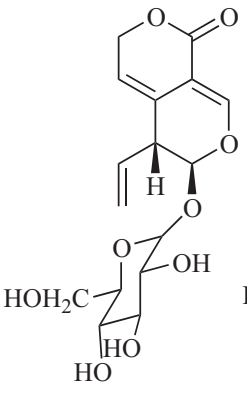
Cynarin

Fig. 14.7

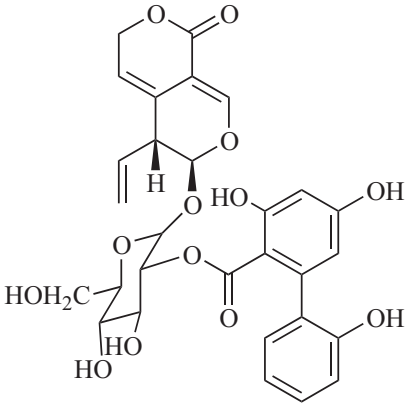
The species is rare (but locally abundant) and distributed in the alpine regions of Europe and western Asia. It is a perennial herb up to 1.4 m high with showy yellow flowers. Because of the high risk of overexploitation (for use as an ornamental and as a medicine) the species is now protected throughout most of its range and attempts are being made to cultivate it. Gentian root in commerce consists of the dried rhizomes and roots of the species. The rhizome is cylindrical and may have a diameter of up to 4 cm, with long roots attached.

Constituents

The compounds responsible for the highly bitter taste are monoterpenoid compounds (Fig. 14.8) such as gentiopicroside – a seco-iridoid with a bitter value of 12,000 – and amarogentin – with a bitter value of 58,000,000, which is only present in minute amounts. The normally white inner part of the rootstock turns yellow during fermentation, due to the formation of xanthones, including gentisin.



Gentiopicroside



Amarogentin

Fig. 14.8

Chemical analysis is carried out following the method of the Eur. Ph., but the 'bitter value' test is also useful. This is a simple and useful measure for establishing the quality of bitter-tasting (botanical) drugs. It is the inverse concentration of the dilution of an extract (or a pure compound) which can still be detected as being bitter to testers with normal bitter taste receptors. In the case of gentian, it should at least be 10,000 (i.e. an extract that has been diluted 10,000 times should still leave a bitter taste).

Therapeutic uses and available evidence

Gentian is indicated for poor appetite, flatulence and bloating, although clinical trial evidence is lacking. Extracts stimulate gastric secretion in cultured rat gastric mucosal cells and gentiopicroside has been shown to suppress chemically and immunologically induced liver damage in mice.

WORMWOOD, *ARTEMISIA ABSINTHIUM* L. (ABSINTHII HERBA) EU

Wormwood is a bitter stimulant derived from the aerial parts of *Artemisia absinthium* (Asteraceae) and is popularly used as a tea. It is a commonly cultivated garden plant. The liqueur was a popular stimulant in many European countries during the latter part of the 19th century and early part of the 20th century, and gave rise to the condition known as absinthism, a form of mental disorder, reputed to affect the artist Van Gogh. The plant is still commonly grown in Mediterranean gardens. The leaves and young stems are densely covered with characteristic greyish-white hairs, which give the species its typical appearance.

A large number of related species are also used as a food (estragon – A. dracunculus) or medicine (*A. annua* L. – the source of artemisinine)

Constituents

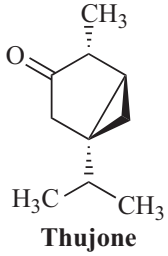
The essential oil contains β-thujone (Fig. 14.9) as the major components, as well as thujyl alcohol, azulenes, bisabolene and others. Sesquiterpene lactones are also present, especially absinthin, anabsinthin, artemetin, artabsinolides A, B, C and D, artemolin and others, and flavonoids. During the process of distillation, the intensively blue chamazulene is formed, which together with the other constituents gives oil of absinth its characteristic green-blue colour. The sesquiterpene lactone absinthin is responsible for the intensive bitter taste, which according to the Eur. Ph. should be at least 10,000 (Deutsches Arzneibuch 15,000) for the crude extract (see 'Gentian' for explanation of bitter value). β-Thujone, a monoterpene, is also partly responsible for the bitterness. The essential oil content should be at least 0.2% and the bitter sesquiterpenoids 0.15–0.4%, according to the Eur. Ph. where the methods are described.

Therapeutic uses and available evidence

It is commonly used as a bitter tonic, a choleretic and also as an anthelmintic. Although its use in the form of a tea is considered safe, the essential oil, and the liqueur 'absinthe' distilled from this plant, are harmful in large doses due to the thujone content, and are not now used except where the thujone has been removed. Most of the evidence is empirical and clinical evidence is limited.

Toxicological risks

Thujone, a major component of the essential oil, is neurotoxic and hallucinogenic in large doses and can produce epileptic fits and long-lasting psychiatric disturbances. These are considered to be a problem only with the distilled ethanolic beverage (absinthe). Thujone is found in the essential oil of many unrelated species, including sage (*Salvia officinalis*) and thuja (*Thuja occidentalis*), and is still used medicinally with few ill-effects. There is also some dispute as to whether 'absinthism' is anything more than plain alcoholism, since thujone levels are not always high enough to be considered as causing such severe damage.



Thujone

Fig. 14.9

NAUSEA AND VOMITING

'Travel sickness' or 'motion sickness' is particularly common in children and is caused by the repetitive stimulation of the labyrinth of the ear. It is most common when travelling by sea, but also happens in cars, aeroplanes and when horse-riding. Vomiting, nausea, dizziness, sweating and vertigo may occur. Prophylactic treatment includes the use of antihistamines (mainly phenothiazines) and cinnarizine, and natural compounds such as the antimuscarinic alkaloid hyoscine, found the Solanaceae family. Morning sickness of pregnancy is also common but few (if any) synthetic drugs are licensed for such a use because of fears of toxicity to the unborn child. Ginger can be a useful anti-emetic for this condition, as well as for travel sickness.

GINGER, *ZINGIBER OFFICINALE* ROSCOE (ZINGIBERIS RHIZOMA) EU

Ginger (Zingiberaceae) is one of the most commonly used culinary spices in the world and has a variety of medicinal uses. The odour and taste are very characteristic, aromatic and pungent. Ginger is cultivated in moist, warm tropical climates throughout south and south-eastern Asia, China, Nigeria and Jamaica. The rhizome is the part used and is available commercially either peeled or unpeeled. African dried ginger is usually unpeeled, and the fresh rhizome, which is widely available for culinary purposes, is always unpeeled. The medicinal use of ginger in Europe has an ancient history and can be traced back to Greek and Roman times. The plant has also been mentioned in Ayurvedic and other religious scriptures dating back to 2000 BC, where it was recognized as an aid to digestion and for cases of rheumatism and inflammation.

Constituents

The rhizome contains 1–3% essential oil, the major constituents of which are zingiberene and β-bisabolene. The pungent taste is produced by a mixture of

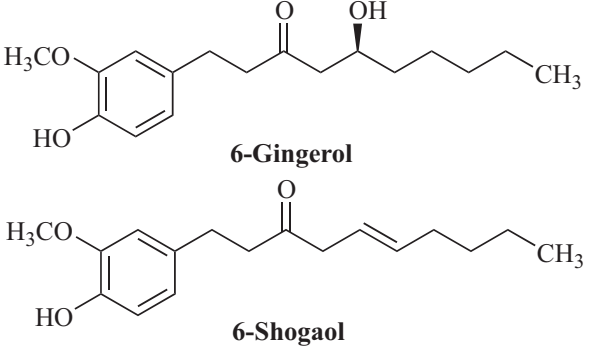


Fig. 14.10

phenolic compounds with carbon side-chains consisting of seven or more carbon atoms, referred to as gingerols, gingerdiols, gingerdiones, dihydrogingerdiones and shogaols (see Fig. 14.10). The shogaols are produced by dehydration and degradation of the gingerols and are formed during drying and extraction. The shogaols are twice as pungent as the gingerols, which accounts for the fact that dried ginger is more pungent than fresh ginger.

Therapeutic uses and available evidence

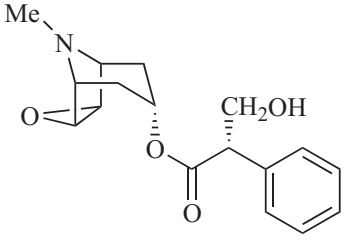
Modern uses of ginger are diverse and include as a carminative, anti-emetic, spasmolytic, antiflatulent, antitussive, hepatoprotective, antiplatelet aggregation and hypolipidaemic. Some of these actions are substantiated by pharmacological *in vivo* or *in vitro* evidence. Of particular importance is the use in preventing the symptoms of motion sickness and postoperative nausea, as well as vertigo and morning sickness of pregnancy, and there is some clinical evidence for the efficacy of ginger in these conditions (Matthews et al 2010). Ginger consumption has also been reported to have a beneficial effect in alleviating the pain and frequency of migraine headaches, and studies on the action in rheumatic conditions have shown a moderately beneficial effect. Anti-ulcer activity has been described in animals and attributed to the volatile oil, especially the 6-gingesulfonic acid content, and hepatoprotective effects have been noted in cultured hepatocytes, with the gingerols being more potent than the homologous shogaols found in dried ginger. Both groups of compounds are antioxidants and possess free radical scavenging activity. Ginger is well known to produce a warming effect when ingested, and the pungent principles stimulate thermogenic receptors. In addition, zingerone induces catecholamine secretion from the adrenal medulla (for review, see Ali et al 2008). In Oriental medicine, ginger is so highly regarded that it forms an ingredient of about half of all multi-item prescriptions. A distinction is made between the indications for the fresh rhizome (vomiting, coughs, abdominal distension and pyrexia) and the dried or processed rhizome (abdominal pain, lumbago and diarrhoea). This is probably justifiable since the constituents are present in different proportions in the different preparations. Ginger, both in the fresh and dried form, is generally regarded as safe.

HYOSCINE (SCOPOLAMINE)

The alkaloid hyoscine (Fig. 14.11) is usually isolated from *Datura* or *Scopolia* spp., although, as the name suggests, it has originally been found in *Hyoscyamus niger*. It is a popular remedy for motion sickness, given at an oral dose of 400 μg or, more recently, as a transdermal patch containing 2 mg of the alkaloid, which is delivered through the skin over 24 h. Hyoscine is also used as a premedication, usually in combination with an opiate, to relax the patient and dry up bronchial secretions prior to administration of halothane anaesthetics.

IRRITABLE BOWEL SYNDROME, BLOATING AND FLATULENCE

Irritable bowel syndrome (IBS) is characterized by pain in the left iliac fossa, diarrhoea and/or constipation. Symptoms are usually relieved to some extent by defecation or the passage of wind, and can be treated successfully by the use of bulk laxatives with or without antispasmodic (carminative) drugs. Natural remedies include peppermint oil and other essential oil carminatives, and some of the tropane alkaloids. Atropine has been replaced



(–) Hyoscine

Fig. 14.11

by hyoscine, in the form of the *N*-butyl bromide, which, as a quaternary ion, is poorly absorbed from the GI tract and, therefore, has fewer anti-muscarinic side effects. Artichoke extract is also useful in irritable bowel syndrome (Walker et al 2001); see under dyspepsia and biliousness.

Flatulence, which is the passage of excessive wind from the body, is a condition for which phytotherapy offers useful therapeutic approaches. Carminatives are usually taken with food; they produce a warm sensation when ingested and promote postprandial elimination of gas. Plant-based carminatives are usually rich in essential oil, such as the fruits ('seeds') of species of the Apiaceae (celery family) and some members of the Lamiaceae (mint family). Many condiments such as cumin and caraway have carminative effects and are used as spices because of their taste *and* their pharmacological effect. The clinical validity of carminatives is based on long historical observation and is well established. The effect of many of these botanical drugs is due to their spasmolytic action, for which some *in vitro* evidence exists (Ford et al 2008), but the precise mechanism of action is unclear. It seems likely that not only is the essential oil responsible for the effect, but that the other components (e.g. the flavonoids) also contribute.

MINT LEAVES AND OILS: *MENTHA* SPECIES

Members of the mint family are widely used for their digestive effects and flavouring qualities. They contain similar compounds, but in differing proportions, which results in subtle differences in their taste and properties.

PEPPERMINT, *MENTHA* × *PIPERITA* L. (MENTHAE PIPERITAE FOLIUM) EU

Peppermint is a hybrid of *Mentha aquatica* and *M. spicata*, which originated spontaneously and has been known for over 2500 years; the first records are from old Egyptian graves (2600–3200 BC). Peppermint has a very characteristic, strongly aromatic and penetrating smell and taste. All species of the genus *Mentha* (the mints) have quadrangular (square) stems and decussate, elongated, dentate leaves with a pointed apex, and pinkish-blue flowers up to 5 mm long, and microscopical characteristics include glandular hairs, which are typical of the Lamiaceae. Both the leaves, in the form of a tea, and the oil are used for digestive problems.

Constituents

Peppermint leaf is rich in essential oil (0.5–4%), the main components being (–)-menthol, menthone, menthylacetate and menthofuran. The plant also contains the non-volatile polyphenolics rosmarinic acid and derivatives, flavonoids and triterpenes.

Peppermint oil is derived from the fresh plant by steam distillation and contains approximately 50% (–)-menthol (Fig. 16.4).

Therapeutic uses and available evidence

Peppermint is often taken in the form of a tea, which provides a refreshing beverage as well as a mild digestive soothing effect (see McKay and Blumberg 2006b). The oil can be given well-diluted with water or as an emulsion (2%, v/v, dispersed in a suitable vehicle) for treating colic and GI cramps in both adults and children, and in the form of enteric-coated capsules for IBS, where it is released directly into the intestine and bowel. The antispasmodic effect of peppermint oil has been well established using a series of *in vitro* models, the effect being marked by a decline in the number and amplitude of spontaneous contractions, and due at least in part to Ca^{2+}-antagonistic effects. Peppermint oil has also been shown clinically to enhance gastric emptying. Peppermint water (or emulsion) is generally safe, although must be used with care. A tragic incident with peppermint water caused the death of a young baby, although the toxicity was due to the excipient rather than to the peppermint oil (by adding concentrated chloroform water rather than the diluted form, two pharmacists inadvertently produced a lethal medication).

JAPANESE MINT, *MENTHA ARVENSIS* L.

Japanese mint is rich in menthol (about 80% of the total volatile oil, see below) and is employed as a cheaper substitute for peppermint or for extraction of menthol.

SPEARMINT, *MENTHA* × *SPICATA* L., SYN. *M. CRISPA*, *M. SPICATA* SUBSP. *CRISPA*

Spearmint gives toothpaste, mouthwash and chewing gum their typical taste and smell. It is an important flavouring agent, but is of limited

pharmaceutical importance. Material from this species is easily identifiable from the taste and odour.

UMBELLIFEROUS FRUITS

The fruits (not 'seeds' as they are commonly known) of several members of the celery family (Apiaceae or Umbelliferae) are used as carminatives as they are rich in essential oil and have an antispasmodic effect. Many of these species are also important as spices. Flower heads of these species are umbels of white or pinkish flowers, which produce the characteristic schizocarp (double) fruits, in which two mericarps are united to form an easily separated fruit on a carpophor (a stalk which means 'carrier of fruit').

CARAWAY, *CARUM CARVI* L. (CARVI FRUCTUS) EU

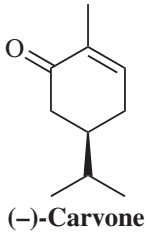
Caraway is the fruit of a mountain herb common in many regions of Europe and Asia.

Constituents

The essential oil (3–7%) consists mainly of (+)-Carvone and (+)-limonene, accounting for 45–65% and 30–40%, respectively, of the total oil. Carvone (Fig. 14.12) is considered to be the main component responsible for the spasmolytic action.

Therapeutic uses and available evidence

The fruits are used in cases of dyspepsia, minor GI cramps and flatulence. Little modern clinical evidence is available but caraway has long been used in products such as infant gripe water. The aqueous extract, and even more so the essential oil, acts as a spasmolytic and has antimicrobial activity.



(–)-Carvone

Fig. 14.12

FENNEL, *FOENICULUM VULGARE* MILLER (FOENICULI FRUCTUS) EU

The common fennel is a perennial herb yielding fruit and oil that are used for stomach and abdominal discomfort, as well as a spice in sweets and liqueurs. Other varieties yield the commonly used vegetable fennel. Two pharmaceutically important varieties are distinguished: *Foeniculum vulgare* var. *dulce* (sweet fennel), which is richer in anethole and has a sweet and aromatic taste, and *F. vulgare* var. *vulgare* (bitter fennel), which is rich in fenchone, resulting in a bitter taste. The two varieties are nearly impossible to distinguish microscopically; consequently, taste and smell differentiation, as well as thin layer chromatography (TLC) analysis, are essential for differentiating the two.

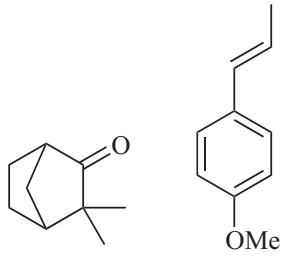
Constituents

All of the aerial parts of fennel are rich in essential oil, with bitter fennel fruit containing 2–6%, mostly *trans*-anethole (>60% of the oil) and fenchone (>15%) (Fig. 14.13), and sweet fennel containing 1.5–3%, composed of *trans*-anethole (80–90%) but with very little fenchone (<1%). Fatty oil and protein are also found in fennel fruit.

Therapeutic uses and available evidence

Fennel is used empirically as a carminative, for indigestion and colic in children. It is considered to be a very safe drug and is widely used as a health-food supplement as well as a spice. Fennel oil (the distilled essential oil of both varieties of fennel) is used for the same indications and has been shown to be bacteriostatic.

Other fruit drugs used for these indications are anise (Anisi fructus) from *Pimpinella anisum*, star anise (Anisi stellata fructus) from *Illicium verum*

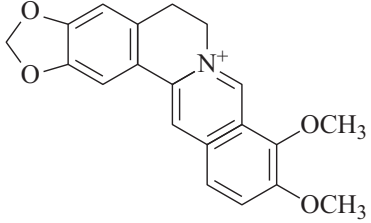


Fenchone Anethole

Fig. 14.13

and coriander (Coriandri fructus) from *Coriandrum sativum*. These agents are all in the Eur. Ph.

The oils of all of these fruits are the subject of monographs in the Eur. Ph. where quantification of compounds is achieved after separation by gas chromatography. Differentiation between the two types of fennel is possible using the TLC method described in the Eur. Ph. where bitter fennel shows an additional yellow zone after spraying with sulphuric acid.



Berberine

Fig. 14.14

LIVER DISEASE

Liver damage, cirrhosis and poisoning should only be treated under medical supervision. There is, however, a useful phytomedicine derived from the milk thistle, *Silybum marianum* (L.) Gaertn. (Asteraceae), in the form of an extract known as silymarin. Other herbs, as shown below, are widely used for liver disease, although with less clinical evidence in support. Herbs used for 'biliousness' (see section on Dyspepsia and Biliousness) are also used in mild liver disease.

ANDROGRAPHIS, *ANDROGRAPHIS PANICULATA* NEES (ANDROGRAPHIS HERBA) EU

Andrographis is widely used in many Asian systems of medicine to treat jaundice and liver disorders. There are few clinical studies available to support these uses, although numerous *in vitro* experiments have shown it has liver protective effects against a variety of hepatotoxins. 14-deoxyandrographolide, a constituent, desensitizes hepatocytes to TNF-alpha-induced signalling of apoptosis (Roy et al 2010). It appears to be well-tolerated but caution should be exercised when given in conjunction with antithrombotic drugs. In the West, it is more often used as an immune stimulant (see Chapter 16, Respiratory System, for more detail, including constituents).

BERBERIS SPECIES AND OTHER BERBERINE-CONTAINING DRUGS

Berberine (Fig. 14.14) is contained in *Berberis* species, for example *B. vulgaris* L., *B. aristata* DC, in Blood root, *Sanguinaria canadensis* L., Goldenseal, *Hydrastis canadensis* L., Gold Thread, *Coptis chinensis* Franch, and Greater Celandine, *Chelidonium majus* L.

Berberine has antibacterial and amoebicidal properties and is used either in the form of the pure compound or as a component of plant extracts, to treat dysentery and liver disease (Imanshahidi and Hosseinzadeh 2008). Care should be taken when given together with anticancer drugs and with ciclosporin, since theoretical drug interactions have been described for these combinations, and berberine is known to be a substrate of P-glycoprotein and to affect expression of cytochrome P(CYP) 450 enzymes 3A4 and others.

MILK THISTLE, *SILYBUM MARIANUM* (SILYBI MARIANAE FRUCTUS) EU

The seeds of the milk thistle, *Silybum marianum* (L.) Gaertn. (Asteraceae), yield a flavolignan fraction known as silymarin.

Constituents

The active constituents of the extract silymarin are flavolignans, mainly silybin (=silibinin), with isosilybin, dihydrosilybin, silydianin, silychristin and others.

Therapeutic uses and available evidence

In many parts of Europe, silymarin is used extensively for liver disease and jaundice. It has been shown to exert an antihepatotoxic effect in animals against a variety of poisons, particularly those of the death cap mushroom *Amanita phalloides*. This fungus contains some of the most potent liver toxins known (the amatoxins and the phallotoxins), both of which cause fatal haemorrhagic necrosis of the liver. Silymarin has been used at doses of 420 mg daily to treat patients with chronic hepatitis and cirrhosis; it is also partially active against hepatitis B virus, is hypolipidaemic and lowers fat deposits in the liver in animals. This extract can be used not only for serious liver disease, but also for general biliousness and other digestive disorders (see Saller et al 2008).

SCHISANDRA, *SCHISANDRA CHINENSIS* K. KOCH (SCHISANDRAE CHINENSIS FRUCTUS) EU

Schisandra (Schizandra) berries are the fruit of the Magnolia Vine, and are very important in traditional Chinese medicine where they are used to treat liver disorders and many other conditions of general debility. Related species are also used.

Constituents

The active constituents are dibenzocyclooctene lignans, known as schisandrins (schizandrins) and gomisins. The nomenclature is confused and, for example, 'schisandrin' is sometimes referred to in the literature as 'schisandrol A', and 'gomisin A' as 'schisandrol B'.

Therapeutic uses and available evidence

A great deal of research has been carried out on the pharmacology of this plant (see review by Panossian and Wikman 2008), and liver protectant effects have been observed in animals, but clinical studies are lacking

TURMERIC, *CURCUMA DOMESTICA* VAL. (CURCUMAE DOMESTICAE RHIZOMA) EU

Turmeric is used in Asian medicine to treat liver disorders and well as inflammatory conditions. For details regarding the drug and its constituents, see Chapter 21 (Musculoskeletal system). Related species include Javanese turmeric (*Curcuma xanthorrhiza* Roxb., Eur. Ph.), which is mostly used for dyspepsia and other gastrointestinal problems. Turmeric and the curcuminoids are hepatoprotective against liver damage induced by various toxins, including paracetamol (acetaminophen), aflatoxin and cyclophosphamide; they protect against stomach ulcers in rats, and have antispasmodic effects. Turmeric is also hypoglycaemic in animals, and hypocholesterolaemic effects have been observed both in animal and human clinical studies, although clinical studies for liver disease are lacking. In addition, turmeric is antibacterial and antiprotozoal *in vitro*. Turmeric is well tolerated but the bioavailability is poor and daily doses of at least 2g are normally used. For reviews see, Rivera-Espinoza and Muriel (2009) and Epstein et al (2010).

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The cardiovascular system

Cardiovascular (CV) disorders are responsible for many deaths in the Western world, and are a consequence of lifestyle and diet, as well as being hereditary to some extent. Serious conditions such as heart failure should be treated only under the guidance of a qualified physician, but some minor forms of CV disease respond well to changes in diet and taking more exercise, as well as phytotherapy. Cardiology has benefited greatly from the introduction of some newer semi-synthetic drugs based on natural products, including aspirin, an antiplatelet agent derived from salicin, and warfarin, an anticoagulant derived from dicoumarol. Others have been developed using a natural product as a template, for example, verapamil, a calcium channel antagonist used to treat hypertension and angina, is based on the opium alkaloid papaverine, and nifedipine, a calcium channel antagonist and amiodarone, an anti-arrhythmic, were both developed from khellin, the active constituent of *Ammi visnaga*. Cocaine has cardioactive as well as central nervous system effects, and was the starting material for the development of the anti-arrhythmics procaine and lignocaine, which are more effective and without the unwanted stimulant activity (Hollmann 1992).

Cardiovascular conditions discussed here include heart failure, venous insufficiency, thrombosis and atherosclerosis. Other conditions such as hypertension and cardiac arrhythmias are rarely treated with phytomedicines, although there are some natural products used in their treatment which will be mentioned briefly. Synthetic diuretics are widely used as antihypertensives, but phytomedicines are not suitable for this purpose as they are not sufficiently potent to reduce blood pressure. Instead, they are often incorporated into remedies for urinary tract complaints (see Chapter 20) or to reduce bloating (mild water retention, for example pre-menstrual).

HEART FAILURE AND ARRHYTHMIAS

These conditions can be treated with cardiac glycosides (cardenolides and bufadienolides) such as digoxin, isolated from the foxglove. Lily of the valley (*Convallaria majalis*) contains convallotoxin (a mixture of cardenolides), and squill (*Drimys maritima*) contains the bufadienolides scillaren A and proscillaridin, but these are rarely used now. Ouabain, isolated from *Strophanthus* spp., has been used in emergency cases. The cardiac glycosides have a positive inotropic effect, meaning that they increase the force of contraction of the heart. They are emetic and toxic in large doses and have a cumulative effect and are, therefore, unsuitable for use in the form of herbal extracts. Single isolated compounds for which the pharmacokinetics can be monitored are used instead.

There are, however, other herbal drugs that have beneficial effects upon the heart, the most important of which are hawthorn (*Crataegus*) and motherwort (*Leonurus cardiaca*). Hawthorn has anti-arrhythmic activity, and will be discussed briefly below. There is not enough evidence available at present to justify the inclusion of motherwort. In general, however, arrhythmias are treated with isolated compounds, most of which are synthetic, although quinidine (an alkaloid from *Cinchona* spp.; Fig. 15.1) is still

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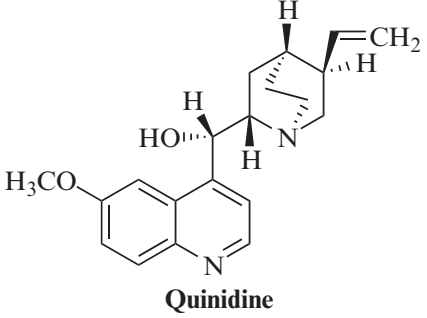


Quinidine

Fig. 15.1

used occasionally. Ajmaline, from *Rauvolfia* spp., is used as an anti-arrhythmic in some parts of the world; sparteine, from broom (*Cytisus scoparius*), was formerly employed. Both of these compounds are alkaloids.

FOXGLOVE (DIGITALIS) LEAF, *DIGITALIS PURPUREA* L. (DIGITALIS PURPUREAE FOLIUM) EU

The purple foxglove (*Digitalis purpurea*) and its close relative the woolly foxglove (*D. lanata* L., Scrophulariaceae), yield cardiac glycosides. These plants are very common; they are indigenous to Europe and cultivated elsewhere. They do not have a long history of herbal use because of their toxicity, although the famous surgeon William Withering described their use for 'dropsy' (an old term for congestive heart failure) in 1870, and this was the first time an effective treatment for this condition had been found. The leaves are the source of the drug and are usually gathered in the second year of growth.

Constituents

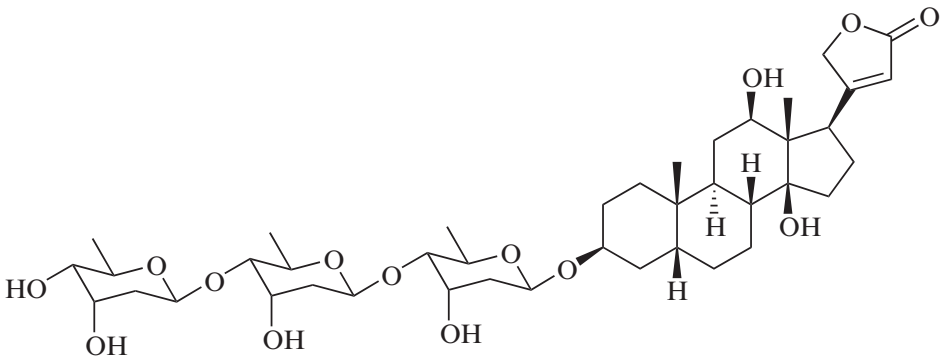
Both species contain cardenolides, which are glycosides of the steroidal aglycones digitoxigenin, gitoxigenin and gitaloxigenin. There are very many cardiac glycosides, but the most important is digoxin (Fig. 15.2) and to a much lesser extent digitoxin, and the purpurea glycosides A and B. *Digitalis lanata* contains higher concentrations of glycosides, including digoxin and lanatosides, and is the main source of digoxin for the pharmaceutical industry.

Therapeutic uses and available evidence

Digoxin increases the force of myocardial contractility and reduces conductivity within the atrioventricular node. It is used primarily in the treatment of supraventricular tachycardia and heart failure and is given as a once-daily dosage in the range 62.5–250 μg. Digitalis glycosides increase the force of contraction of the heart without increasing the oxygen consumption, and slow the heart rate when atrial fibrillation is present. Due to their cumulative effect, the glycosides can easily give rise to toxic symptoms, such as nausea, vomiting and anorexia, especially in the elderly, thus blood levels should be monitored.

HAWTHORN, *CRATAEGUS* SPP. (CRATAEGI FOLIUM CUM FLORE, CRATAEGI FRUCTUS) EU

Hawthorn is a common plant found in hedgerows and gardens throughout Europe and elsewhere; it is sometimes known as mayflower or whitethorn. The flowers, leaves and berries of at least two species are used: *Crataegus oxycanthoides* Thuill. and



Digoxin

Fig. 15.2

C. monogyna Jacq. (Rosaceae). These are hairless, thorny, deciduous shrubs with 3–5 lobed leaves, bearing white, dense clusters of flowers, followed by deep red fruits containing one seed (in *C. monogyna*) or two seeds (in *C. oxycanthoides*). The flowers appear in early summer and the berries or 'haws' in early autumn. Jams and wines are often made from the fruit.

Constituents

The main constituents of the leaf are flavonoids, including vitexin, vitexin-4-rhamnoside, quercetin and quercetin-3-galactoside, hyperoside, rutin, vicentin, orientin; the fruit contains flavonoids, procyanidins, catechins and epicatechin dimers, as well as phenolic acids such as chlorogenic and caffeic acids. Amines such as phenethylamine and its methoxy derivative, as well as dopamine, acetylcholine and tyramine, have also been isolated. It is thought that a mixture of active constituents may be necessary for the therapeutic effect. The drug prepared from hawthorn is often standardized to contain 4–30 mg of flavonoids, calculated as hyperoside, or 30–160 mg of procyanidins, calculated as epicatechin. In the Eur. Ph., the leaf and flower, and also the berries, are identified using thin layer chromatography (TLC) with the hyperoside, rutin and chlorogenic acid as reference standards. The assays are different, however; whereas the leaf and flower use the flavonoid content, the berries are assayed for anthocyanin content.

Therapeutic uses and available evidence

Hawthorn is used as a cardiac tonic, hypotensive, coronary and peripheral vasodilator, anti-atherosclerotic and anti-arrhythmic. Animal studies have shown beneficial effects on coronary blood flow, blood pressure and heart rate, as well as improved circulation to the extremities (Alternative Medicine Review (Crataegus) 2010). Hawthorn extract inhibits myocardial Na^+, K^+-ATPase and exerts a positive inotropic effect and relaxes the coronary artery. It blocks the repolarizing potassium current in the ventricular muscle and so prolongs the refractory period, thus exerting an anti-arrhythmic effect. It seems to protect heart muscle by regulating Akt and HIF-1 signalling pathways (Jayachandran et al 2010), and reducing oxidative stress (Bernatoniene et al 2009, Swaminathan et al 2010). There are as yet few clinical trials of the drug, although a recent double-blind pilot study indicated a promising role for hawthorn extract in mild essential hypertension (Walker et al 2002). However, other studies have found that tolerance to exercise was not improved in patients with class II congestive heart failure (Zick et al 2009). It seems likely that hawthorn can be used as an adjunct or sole treatment only in milder cases of heart disease. The usual recommended dose of standardized extract (see Constituents, above) is 160–900 mg daily. Few side effects have been observed, and both patients and physicians rated the tolerance of the drug as good, although nausea and headache have been reported infrequently.

VENOUS INSUFFICIENCY AND CIRCULATORY DISORDERS

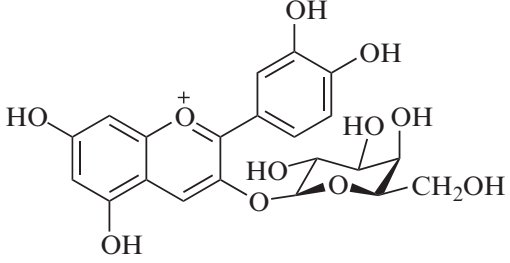
Improvements in circulatory disorders arise from a number of different pharmacological effects, particularly those involving anti-inflammatory and antioxidant activity. Plant drugs with these actions are important in the treatment of haemorrhoids, varicose veins, impaired visual acuity and even in memory enhancement, when blood flow to the brain may be affected. They usually contain saponins with anti-inflammatory activity, or anthocyanidins and other antioxidants. The most important are bilberry, butcher's broom, horse chestnut, ginkgo and garlic.

BILBERRY, *VACCINIUM MYRTILLUS* L. (MYRTILLI FRUCTUS) EU

The bilberry, also known as the huckleberry or blueberry (*Vaccinium myrtillus* L., Vacciniaceae), grows on acid soil in hilly and mountainous regions of Europe, Asia and North America. It is cultivated extensively for its delicious fruit, which ripen from July to September. The soft blue-black berries, about 0.51 cm in diameter, have a persistent calyx ring at the apex and contain numerous small oval seeds. Both the ripe fruit and the leaves are used medicinally.

Constituents

The fruit contains anthocyanosides (Fig. 15.3), mainly galactosides and glucosides of cyanidin, delphidin and malvidin, together with vitamin C and volatile flavour components such as *trans*-2-hexenal and ethyl-2- and -3-methylbutyrates. Unlike other *Vaccinium* spp., bilberry does not contain arbutin or other hydroquinone derivatives. The anthocyanins can be estimated using their absorption at 528 nm, as described in the Eur. Ph.



Cyanidin-3-O-galactoside

Fig. 15.3

Therapeutic uses and available evidence

The berries were traditionally used as an antidiabetic, and an astringent and antiseptic for diarrhoea. However, bilberry is now more important as an agent to improve blood circulation in venous insufficiency, especially for vision disorders such as retinopathy caused by diabetes or hypertension. The anthocyanosides are mainly responsible for these properties, due to their antioxidant and free radical scavenging properties. Other cardiovascular benefits include antiplatelet and anti-atherosclerotic effects. Bilberry extracts have a spasmolytic action on the gut and inhibit certain proteolytic enzymes. Anti-inflammatory, antiulcer effects have also been noted, and many of these have been supported by clinical studies (e.g. Christie et al 2001), although the quality of the trials for improving vision have been criticised for their methodology (Canter and Ernst 2004). The usual daily dose of a standardized anthocyanoside extract of bilberry is 480 mg, taken in divided doses. Few side effects have been observed, as would be expected of a widely consumed food substance.

BUTCHER'S BROOM, *RUSCUS ACULEATUS* (RUSCI RHIZOMA) EU

Butcher's broom (*Ruscus aculeatus* L., Liliaceae) is an evergreen shrub native to Europe, and is found in dry woods and among rocks. It is often cultivated for its tough, spiky twigs and 'leaves', which can be preserved and used for decoration. The true leaves are reduced to small scales and the stems flattened at the ends into oval 'cladodes' which resemble leaves, each bearing a small white flower in the centre, followed by a round scarlet berry, and ending in a sharp spine. The rhizome or whole plant can be used.

Constituents

Actives are saponin glycosides, including ruscine and ruscoside, aculeosides A and B, which are based on ruscogenin (1β-hydroxydiosgenin) and neoruscogenin.

Therapeutic uses and available evidence

Butcher's broom has anti-inflammatory effects and is used mainly for diseases of venous insufficiency, such as varicose veins and haemorrhoids. The ruscogenin constituents have been shown to reduce vascular permeability and improve symptoms of retinopathy and lipid profiles of diabetic patients. The extract is either taken internally as a decoction or, more often, applied topically in the form of an ointment (or a suppository in the case of haemorrhoids). The saponins inhibit elastase activity *in vitro* and for this reason extracts are widely used in cosmetic preparations (Redman 2000). When applied topically, few side effects have been observed, apart from occasional irritation.

GINKGO, *GINKGO BILOBA* (GINKGO FOLIUM) EU

See Chapter 17 for more detail about the plant. *Ginkgo biloba* can also be used in cases of peripheral arterial occlusive disease and other circulatory disorders. Although probably less potent than some synthetic drugs, it has the advantage of being well tolerated. Ginkgo improves blood circulation and can alleviate some of the symptoms of tinnitus, intermittent claudication and altitude sickness. Ginkgo extracts have complex effects on isolated blood vessels. The ginkgolides are specific platelet-activating factor (PAF) antagonists and inhibit effects produced by PAF, including platelet aggregation and cerebral ischaemia. The usual dose is 120–160 mg of extract daily.

HORSE CHESTNUT, *AESCULUS HIPPOCASTANEUM* L. (HIPPOCASTANI SEMEN) EU

Aesculus hippocastaum (syn. *Hippocastanum vulgare*, Gaertn., Hippocastanaceae) is native to western Asia, but is now cultivated and naturalized in most temperate regions. It is a large tree, bearing large sticky leaf buds, which open in early spring. The leaves are composed of 5–7 large oval leaflets; the flowers have a candle-like appearance and are white or pink in colour. The bark is thick, rough,

grey or brown on the external surface and pinkish-brown and finely striated on the inside. The fruits are spiny capsules, each with two to four compartments containing the well-known large shiny brown seeds or 'conkers'. The seeds, and occasionally the bark, are used.

Constituents

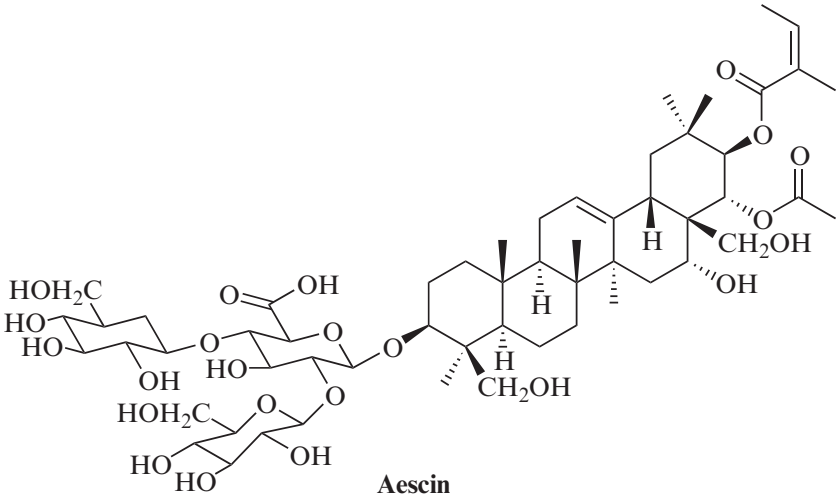
Both contain a complex mixture of saponins based on protoescigenin and barringtogenol-C, which is sometimes known as 'aescin' (or 'escin'), although this term refers more properly to the isomeric compound aescin (see Fig. 15.4). More than 30 saponins have been identified, including α- and β-escin, together with escins Ia, Ib, IIa, IIb, IIIa, etc. Sterols and other triterpenes such friedelin, taraxerol and spinasterol are present, as well as coumarins (e.g. esculin=aesculin) and fraxin, flavonoids and anthocyanidins.

Therapeutic uses and available evidence

Extracts of horse chestnut, or, more usually, extracts standardized to the escin content, are used particularly for conditions involving chronic venous insufficiency (CVI), bruising and sports injuries. They can be taken internally or applied topically. A number of clinical studies have shown benefits in CVI (Pittler and Ernst 2006), deep vein thrombosis (DVT), including after surgery, varicose veins (including those of pregnancy) and for the prevention of oedema during a long (15 h) aeroplane flight. It was found to be beneficial in the treatment of cerebral oedema following road accidents. Venotonic effects, and an improvement in capillary resistance, have also been noted in healthy volunteers (Suter et al 2006). Escin has been shown to reduce oedema, decrease capillary permeability and increase venous tone, and horse chestnut extract to contract both veins and arteries *in vitro*, with veins being the more sensitive. The extract also significantly reduced ADP-induced human platelet aggregation, and these effects appear to be at least partly mediated through 5-HT(2A) receptors (Felixsson et al 2010). Horse chestnut extract also antagonizes some of the effects of bradykinin and produces an increase in plasma levels of adrenocorticotrophin, corticosterone and glucose in animals. Escin is widely used in cosmetics. The usual dose is 600 mg of extract daily, which corresponds to about 100 mg of escin. Extracts are well tolerated at therapeutic doses, but higher amounts can cause gastrointestinal upset with internal use, and occasional irritation with external application.

RED ROOT SAGE, *SALVIA MILTIORRHIZA* L. (SALVIAE MILTIORRHIZAE RADIX)

The root and rhizome of *Salvia miltiorrhiza* Bunge, also known as Danshen, are widely used in traditional Chinese medicine to treat many types of cardiovascular diseases, including ischaemic and circulatory disorders such as angina, after stroke and atherosclerosis. The root has a characteristic bright red colour, which is due to the active constituents, the tanshinones.



Aescin

Fig. 15.4

Constituents

The main active constituents are diterpene quinones, known as tanshinones (one of the transliterations of *danshen* is *tan-shen*, hence the quinones were called tanshinones). Tanshinone I, tanshinone II, cryptotanshinone are the major constituents, although nearly 40 variants of the basic tanshinone structures have been found in the roots. The total tanshinone content of the roots is about 1%, with tanshinone I and II and cryptotanshinone being the major components.

Therapeutic uses and available evidence

Animal studies have shown many relevant effects, such as protecting heart muscle from ischaemia and improving microcirculation. The isolated tanshinones have been shown to reduce fever and inflammation, inhibit platelet aggregation, dilate the blood vessels and aid urinary excretion of toxins. *Salvia miltiorrhiza* has a mild vasodilatory effect but does not increase cardiac output. Clinical studies carried out in China have shown benefit to patients with heart and circulatory diseases, including ischaemic stroke and acute myocardial infarction, but many of these do not fulfil the criteria required for acceptance in the West, and the efficacy has, therefore, not been accepted there (Wu et al 2007, Wu et al 2008, Yu et al 2009). In general, *Salvia miltiorrhiza* seems to be safe and well-tolerated at the usual dose of 2–6 g day for the dried root, or equivalent in the form of an extract, but there is a potential for drug interactions, especially with other cardiovascular drugs (Williamson et al 2009).

RED VINE LEAF, *VITIS VINIFERA* L. (VITIS VINIFERAE FOLIUM)

Certain varieties of grape vine (*Vitis vinifera* L., a plant which needs no description) produce red leaves which are used in the treatment of CVI and, in particular, varicose veins. Unusually, however, the definition of the botanical drug not only covers the species and a certain plant part, but also the use of a specific prominently coloured variety.

Constituents

Grape leaves contain a wide range of polyphenols including quercetin-3-O-beta-D-glucuronide and isoquercetrin (the main flavonoids), anthocyanins, oligomeric proanthocyanidins, catechin, epicatechin monomers and dimers, gallic acid and astilbine. The phytoalexin trans-resveratrol, another polyphenolic substance belonging to the stilbene group, can also be found in grape vine, organic acids, mainly malic and oxalic acid. The dried leaves of red vine should contain at least 4% of total polyphenols and 0.2% of anthocyanins.

Therapeutic uses and available evidence

Clinical studies have shown that the extract can improve objective symptoms of CVI and that it may prevent further CVI deterioration (Kalus et al 2004). Red vine leaf extracts are also used to improve the microcirculation and aid wound healing (Wollina et al 2006). *In vitro* studies indicate that they have antioxidant and anti-inflammatory properties, and that they inhibit platelet aggregation and hyaluronidase, and reduce oedema, possibly by reducing capillary permeability. Preclinical *in vivo experiments* demonstrated anti-inflammatory and capillary wall thickening effects.

Red vine leaf extract can be applied topically and taken internally, and is well-tolerated, although minor gastrointestinal effects have been reported. Commercial products are usually standardized to 90% polyphenols and 5% astilbine, with a daily dose of 360 mg red vine leaf extract being the recommended internal dose.

ANTIPLATELET AND ANTI ATHEROSCLEROTIC DRUGS

Thrombosis and atherosclerosis are the result of a sedentary lifestyle and high sugar and fat consumption. Their incidence is rising and the age at which patients show signs of these conditions is getting younger. These conditions are closely related in that atherosclerosis predisposes to thrombus formation, and can result in peripheral arterial disease, myocardial infarction and stroke. As well as improving diet and taking regular exercise, preventative drugs can be taken, many of which are natural products of some kind. Antiplatelet drugs are used prophylactically to decrease platelet aggregation and inhibit thrombosis. The standard antiplatelet drug is aspirin, which is used in doses that are lower (75–300 mg daily) than for pain relief (300 mg to 1 g, up to four times daily).

Many items of diet also have antiplatelet effects, for example the flavonoids and anthocyanidins, as well as garlic, which is used as a food supplement for this and other purposes (e.g. as an antimicrobial). Garlic also has anti-atherosclerotic effects and is part of the 'Mediterranean diet' or the 'French paradox', in which there is a generally lower incidence of heart disease despite a cuisine rich in cream and butter. Other elements of this diet include olive oil, which contains monounsaturated fatty acids, which also lower blood cholesterol levels, and red wine, which contains anthocyanidins (see bilberry, above).

Ginkgo has antiplatelet activity and is used to improve peripheral blood circulation; this has a beneficial effect on memory and cognitive processes and will be discussed in more detail in Chapter 25. Generally these medicines are very safe, but care should be taken if they are used in conjunction with anticoagulants or prior to surgery. High-fibre phytomedicines, also used as bulk laxatives such as ispaghula and psyllium husk, lower plasma lipid levels and can be used as adjuncts to a low-fat diet. Oat bran (*Avena sativa*) and guar gum (*Cyamopsis tetragonolobus*; see also Chapter 19) lower cholesterol levels; these are thought to act by binding to cholesterol Weinmann et al 2010.

GARLIC, *ALLIUM SATIVUM* L. (ALLII SATIVI BULBUS) EU

The garlic bulb (*Allium sativum*, Liliaceae) is composed of a number of small bulbs or 'cloves', covered with papery, creamy-white bracts. Garlic is cultivated worldwide and is used in many forms of cooking. The drug in commerce is the powder prepared from the cut, dried or freeze-dried bulb.

Constituents

Garlic contains a large number of sulphur compounds which are responsible for the flavour and odour of garlic, as well as the medicinal effects. The main compound in the fresh plant is alliin, which on crushing undergoes enzymatic hydrolysis by alliinase to produce allicin (S-allyl-2-propenthiosulphinate; Fig. 15.5). This in turn forms a wide range of compounds such as allylmethyltrisulphide, diallyldisulphide, ajoene and others, many of which are volatile. Sulphur-containing peptides such as glutamyl-*S*-methylcysteine, glutamyl-*S*-methylcysteine sulphoxide and others are also present.

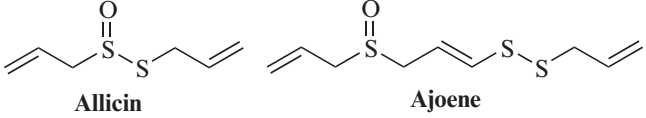


Fig. 15.5

Therapeutic uses and available evidence

Different types of garlic preparations are available, such as standardized allicin-rich extracts, aged garlic extracts (particularly in the Far East) and capsules containing the oil (older products). All have different compositions, but it is recognized that the sulphur-containing compounds must be present for the therapeutic effect. Deodorized products, except for those containing the precursor allicin, are ineffective. Hypolipidaemic activity has been observed in animals with garlic extract; this has been attributed to *S*-allylcysteine which is regarded as important in this activity. *S*-Allylcysteine inhibits NF-kB synthesis and low-density lipoprotein (LDL) oxidation, which are both implicated in atherosclerosis. Allicin is also antioxidant, and garlic extracts protect endothelial cells from oxidized LDL damage. It is known that ajoene (Fig. 15.5) is a potent antithrombotic agent, as well as 2-vinyl-4*H*-1, 3-dithiin to a lesser extent. Cardiovascular benefits are supported by the antithrombotic activity, which has been shown in several studies, and an antiplatelet effect demonstrated by aged garlic extracts in humans.

Other health benefits attributed to garlic are antibacterial, antiviral and antifungal effects, and, more importantly, chemopreventative activity against carcinogenesis in various experimental models. Diallylsulphide is thought to inhibit carcinogen activation via cytochrome P450-mediated oxidative metabolism, and epidemiological evidence suggests that a diet rich in garlic reduces the incidence of cancer. Hepatoprotection against paracetamol (acetaminophen)-induced liver damage has been described and attributed to similar mechanisms. The evidence for the health benefits of taking garlic is generally good despite the poor quality of some trials (Aviello et al 2009). The usual dose of garlic products is equivalent to 600–900 mg of garlic powder daily. Garlic has few side effects, but due to the antiplatelet effects, care should be taken if given in combination with other cardiovascular drugs.

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The respiratory system

Minor common disorders of the respiratory system can often be successfully treated with phytotherapy and it can be helpful as a supportive measure in more serious diseases, such as bronchitis, emphysema and pneumonia. For severe infections, antibiotic therapy may be needed and, although most antibiotics are natural products, their study is a separate issue and will not be dealt with here. However, for colds and flu-like virus infections, decongestants (e.g. menthol and eucalyptus), broncholytics and expectorants (including ipecacuanha, thyme and senega), demulcents (e.g. mallow), antibacterials and antivirals (e.g. linden and elder flowers, pelargonium) and immune system modulators (e.g. echinacea, andrographis) are popular and effective. Allergic conditions such as hay fever can be treated with butterbur, *Petasites* and, traditionally, a compound of garlic and echinacea is used for allergic and infective rhinitis. Asthma is becoming more prevalent for reasons as yet unknown, but is best treated aggressively with inhaled steroids and bronchodilators. Many bronchodilators are either of natural origin (e.g. theophylline and ephedrine) or have been developed from natural products. Although isolated ephedrine and pseudoephedrine are theoretically contraindicated in asthma because they can precipitate an attack, ephedra herb has a long history of use without apparent ill-effects; this is attributed to other constituents in the whole extract. Antimuscarinic drugs (e.g. atropine), which have bronchodilator effects and also dry up secretions, have largely been superseded by derivatives such as ipratropium. An important compound, sodium cromoglycate, is an anti-allergic drug developed from khellin, which stabilizes mast cells and is used in the form of an inhaler to treat asthma. Platelet-activating factor antagonists (e.g. the ginkgolides) have anti-allergic effects, which may be useful in asthma but are not yet employed clinically. Ginkgo is covered in Chapter 16. Leukotriene antagonists have recently been introduced for asthma therapy and, although no plant products are yet in use, there are several natural compounds (e.g. quercetin) with this property and they may become available in the future. Cough suppressants are very popular, although there is some controversy as to whether they are clinically effective. The most important antitussives are codeine and other opiate derivatives obtained from the opium poppy.

BRONCHODILATORS AND DECONGESTANTS

SYSTEMIC DRUGS

EPHEDRA, *EPHEDRA* SPP. (EPHEDRAE HERBA) EU

Ephedra, also known as Ma Huang (*Ephedra sinica* Stapf. and other species of the family Ephedraceae) is an ancient Chinese medicine, which is now used worldwide. It was the original source of ephedrine, a useful decongestant and bronchodilator. Traditionally, it is used to treat asthma and nasal congestion, in the form of nasal drops. Pseudoephedrine is now used more widely for respiratory congestion as it has fewer central nervous system (CNS) stimulatory properties. The plant has slender green stems, which are jointed in branches of about 20 tufts about 15 cm

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long, and terminate in a sharp, recurved point. These are the medicinal part. The leaves are reduced to sheaths surrounding the stems.

Constituents

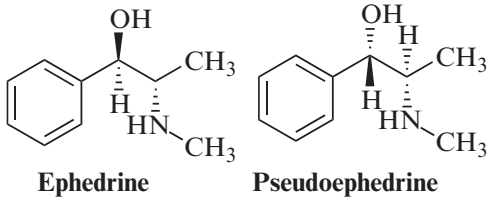
Alkaloids, up to about 3%, but widely varying; the major alkaloid is (–)-ephedrine (Fig. 16.1), together with many others. These include (+)-pseudoephedrine, norephedrine, norpseudoephedrine, ephedroxane, *N*-methylephedrine, maokonine, transtorine and the ephedradines A–D. Other components are catechin derivatives, and diterpenes, including ephedrannin A and mahuannin A, have been isolated from other species of *Ephedra*.

Therapeutic uses and available evidence

Ephedra has been used since ancient times in China for asthma and hay fever, as a bronchodilator, sympathomimetic, CNS and cardiac stimulant. Herbalists also use it to treat enuresis, allergies, narcolepsy and other disorders, and anti-inflammatory activity has been observed in extracts. Ephedrine is used in the form of elixirs and nasal drops, and has an additional use as a heart rate accelerator in the treatment of some types of bradycardia. Pseudoephedrine, the D-isomer of ephedrine produced by chemical synthesis, is usually the compound of choice for isolated alkaloid preparations. Ephedra herb, ephedrine and pseudoephedrine are all the subject of European Pharmacopoeia (Eur. Ph.) monographs. Ephedra herb is used as an anti-allergic agent; this is supported by evidence that it induces immunoglobulin A in Peyer's patches and blocks complement activation by both the classical and alternative pathways.

Toxicological risks

The herb has been abused as a slimming aid, and an ergogenic aid in sports and athletics, but this is dangerous (Fleming 2008). For example, hypertension and other cardiovascular events, and a case of exacerbation of hepatitis, have been noted with high doses.



Ephedrine **Pseudoephedrine**

Fig. 16.1

The absorption of ephedrine and pseudoephedrine is slower after ingestion of the herb than for isolated alkaloid preparations, and the other constituents, the ephedradins, mahuannins and maokonine, are mildly hypotensive; but both the herb and the isolated alkaloids should be avoided by hypertensive patients as well as in cases of thyrotoxicosis, narrow-angle glaucoma and urinary retention. Therapeutic doses of the herb are calculated to deliver up to 30 mg of the alkaloids, calculated as ephedrine.

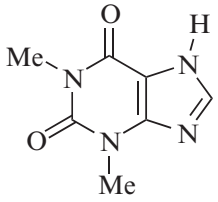
THEOPHYLLINE EU

Although a natural xanthine, theophylline (Fig. 16.2), which is found in cocoa (*Theobroma cacao*), coffee (*Coffea* spp.) and tea (*Camellia sinensis*), is almost invariably used as the isolated compound. It is indicated in reversible airways obstruction, particularly in acute asthma. Because of the narrow margin between the therapeutic and the toxic dose, and the fact that the half-life is highly variable between patients, especially smokers and in heart failure or with concurrent administration of other drugs, care must be taken. The usual dose is 125–250 mg in adults, three times daily, and half of that in children.

Side effects include tachycardia and palpitations, nausea and other gastrointestinal upsets. These can be reduced using sustained-release preparations, and this is the usual form of theophylline products.

INHALATIONS

Essential oil containing drugs are often used with aromatic compounds (especially camphor) as chest rubs, steam inhalations or nasal sprays, for their decongestant properties. They are particularly useful for infants, children, asthmatics and pregnant women for whom systemic decongestants may not be appropriate. They may also be used orally, in pastilles, lozenges, or 'cough sweets'. Oils distilled from the aerial parts of members of the pine family



Theophylline

Fig. 16.2

[e.g. the common Pumilio (Alpine) pine (*Pinus mugo*), the European larch (*Larix decidua*) and the fir tree (*Abies* spp.)] and the Australian Myrtaceae (e.g. eucalyptus and tea-tree oil) are used frequently. These oils can also be used in steam baths.

CAMPHOR EU

Camphor (Fig. 16.3), a pure natural product, is derived from the Asian camphor tree (*Cinnamomum camphora* T. Nees & Eberm., Lauraceae). It is often combined with the essential oil containing drugs as an aromatic stimulant and decongestant.

Camphor has antiseptic, secretolytic and decongestant effects. Small doses were formerly taken internally for colds, diarrhoea and other complaints, but it is now used only externally.

Toxicological risks

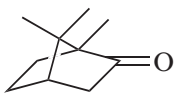
Camphor has been in use for many years; however, 'camphorated oil' was recently taken off the market since, in large quantities, camphor may be absorbed through the skin causing systemic toxicity. Overdose causes vomiting, convulsions and palpitations, and can be fatal. However, when used externally in therapeutic doses it is generally well tolerated.

EUCALYPTUS OIL, *EUCALYPTUS* SPP. (EUCALYPTI AETHEROLEUM) EU

The blue gum tree, *Eucalyptus globulus* Labill., and other species (Myrtaceae) yield a highly characteristic oil which is widely used as a decongestant and solvent. The leaves are scimitar-shaped, 10–15 cm long and about 3 cm wide, shortly stalked and rounded at the base, with numerous transparent oil glands.

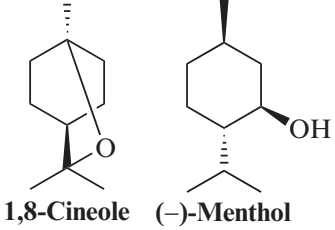
Constituents

The oil contains 1,8-cineole (eucalyptol; see Fig. 16.4) as the major component, with terpineol, α-pinene, *p*-cymene and small amounts of ledol, aromadendrene and viridoflorol, aldehydes, ketones and alcohols.



Camphor

Fig. 16.3



1,8-Cineole (–)-Menthol

Fig. 16.4

Therapeutic uses and available evidence

The oil is antiseptic, antispasmodic, expectorant, stimulant and insect repellent. It is a traditional Australian Aboriginal remedy for coughs, colds and bronchitis. It may be taken internally in small doses (0.05–0.2 ml), as an ingredient of cough mixtures, sweets and pastilles, or as an inhalation; it is applied externally in the form of a liniment, ointment or 'vapour rub'. The leaf extract and oil have well-defined antiseptic effects against a variety of bacteria and yeasts. The oil is also insect-repellent and larvicidal, and is used in pharmaceutical products for these properties as well as for its antiseptic and flavouring properties in dentifrices and cosmetics. It is widely used in Menthol and Eucalyptus Inhalation BP for steam inhalation as a decongestant. Eucalyptus oil is irritant and, although safe as an inhalation, caution should be exercised when taken internally as fatalities have been reported.

MENTHOL EU

Menthol is a monoterpene (Fig. 16.4) extracted from mint oils, *Mentha* spp. (especially *M. arvensis*) or it can be made synthetically. Whole peppermint oil is used in herbal combinations to treat colds and influenza (as well as for colic, etc.; see Chapter 14), but isolated menthol is an effective decongestant used in nasal sprays and inhalers. Menthol can be irritant and toxic in overdose, but is generally well tolerated in normal usage.

ANTI-ALLERGICS

Most antihistamines are synthetic in origin and, although many flavonoids have anti-allergic properties, they are nowhere near as potent as, for example, cetirizine, desloratidine, fexofenadine or chlorpheniramine. Recently, however, an extract of the herbal drug butterbur (see below) was found

to be equivalent in activity to cetirizine. There is a problem with toxic alkaloids in this plant, which if present must be removed from the product; thus it is not suitable as a home remedy without expert advice. Smooth muscle relaxant drugs have been used widely in asthma, and one of these, khellin (used particularly in the Mediterranean region, and isolated from *Ammi visnaga*), was investigated as a lead compound for development. One derivative, sodium cromoglycate, was discovered to have antiallergic effects (see below).

BUTTERBUR, *PETASITES HYBRIDUS* L.

Petasites hybridus (syn. *P. vulgaris, Tussilago petasites*, Compositae) is a downy perennial, common in damp places throughout Europe, with very large heart-shaped leaves and lilac-pink brush-like flowers which occur in early spring before the leaves appear. The root and herb are used.

Constituents

Butterbur contains sesquiterpene lactones (eremophinolides), including a series of petasins and isopetasins, neopetasin, petasalbin, furanopetasin, petasinolides A and B, and flavonoids including isoquercetin glycosides. However, toxic pyrrolizidine alkaloids (senecionine, integerrimine, senkirkine, petasitine and neopetasitine) may be present, usually in higher concentrations in the root.

Therapeutic uses and available evidence

Butterbur is traditionally used as a remedy for asthma, colds, headaches and urinary tract disorders. It is used as an antihistamine for seasonal allergic rhinitis, and a recent randomized, double-blind comparative study using 125 patients over 2 weeks of treatment showed that butterbur extract is as potent as cetirizine. The anti-inflammatory activity is due mainly to the petasin content. Extracts inhibit leukotriene synthesis and are spasmolytic, and reduce allergic airway inflammation and AHR by inhibiting the production of the Th2 cytokines IL-4 and IL-5, and RANTES (Brattström et al 2010), thus supporting its use in asthma. Use as prophylactic treatment for migraine has also been suggested but further evidence of efficacy is needed (Agosti et al 2006). The usual dose is an extract equivalent to 5–7 g of herb or root. Internal use is not recommended unless the alkaloids are present in negligible amounts or have been removed from preparations, as is the case with the commercially available product, which is a 'special extract'. Maximum intake of the alkaloids should be less than 1 μg daily for fewer than 6 weeks per year.

KHELLA, *AMMI VISNAGA* (L.) LAM.

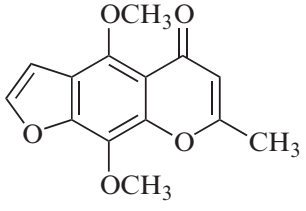
Also known as the 'toothpick plant', as the woody pedicels can be used for this purpose, khella (Apiaceae) is an herbaceous annual reaching 1.5 m in height, with divided filiform leaves and typically umbelliferous flowers. The botanical drug is the fruits, which are very small, broadly ovoid and usually found as separate greyish-brown mericarps. The drug has a long history of use in the Middle East, especially Egypt, as an antispasmodic in renal colic, for asthma and as a coronary vasodilator for angina.

Constituents

Key active principles are furanocoumarins, the most important being khellin (Fig. 16.5), together with visnagin, visnadin and khellol glucoside.

Therapeutic uses and available evidence

Khellin, visnadin and visnagin are vasodilators, with calcium channel blocking and spasmolytic activity. Khellin was the starting material for the development of several important semi-synthetic derivatives such as sodium cromoglycate, which is widely used as a prophylactic treatment for asthma, hay fever and other allergic conditions, often in the form of an inhaler or eyedrops. It was also the basis for the development of nifedipine (a calcium channel antagonist and vasodilator) used in heart disease, and amiodarone, a cardiac antiarrhythmic.



Khellin

Fig. 16.5

EXPECTORANTS AND MUCOLYTICS

The purpose of these drugs is to reduce the viscosity of mucus in the respiratory tract to enable expectoration of phlegm in cases of chest and throat infection. Frequently, essential oils are used with expectorant aromatic compounds such as camphor. Many expectorants are included in cough mixtures and, although efficacy is difficult to demonstrate, these products are very popular with patients in the absence of other treatments. All are used for coughs and colds, bronchitis and sinusitis, usually in conjunction with other decongestants, demulcents, analgesics and, occasionally, antibiotics. Some of these drugs contain essential oils and salicylates (e.g. poplar buds, thyme), and may also include the decongestants mentioned above (eucalyptus, menthol); others contain saponins (e.g. senega, ivy).

BALM OF GILEAD (POPLAR BUDS), *POPULUS* SPP.

Poplar buds (from various *Populus* spp., including *P. candicans* Ait., *P. gileadensis Rouleau*, *P. balsamifera* L. and *P. nigra* L., Salicaceae) are collected in the spring before they open. P. *gileadensis* and *P. nigra* are cultivated in Europe; the others are North American. The buds of all species are similar, being about 2 cm long and 0.5 cm wide, with narrow, brown, overlapping scales; the inner scales are sticky and resinous. The bark of these species is also used.

Constituents

All contain the phenolic glycosides salicin (salicyl alcohol glucoside), populin (benzoyl salicin) and a volatile oil containing α-caryophyllene, with cineole, bisabolene and farnesene. Flavonoids (pinocembrin and pinobanksin) and, in *P. nigra* at least, lignans, based on isolariciresinol, have been isolated.

Therapeutic uses and available evidence

Balm of Gilead is an expectorant, stimulant, antipyretic and analgesic. It is a common ingredient of herbal cough mixtures, and also ointments used for rheumatic and other muscular pains. The phenolic glycosides (e.g. salicin) and the volatile oil constituents have antiseptic and expectorant activity. Little evidence is available for efficacy, but the drug has a long history of traditional use. The bark of poplar species is used in a similar way to willow bark, as an antirheumatic.

Balm of Gilead is generally non-toxic, except for patients who are allergic to salicylates. If excessive amounts of these drugs are taken, adverse effects such as stomach upset and tinnitus are possible, due to the salicylate content.

THYME AND WILD THYME, *THYMUS VULGARIS* L. AND *THYMUS SERPYLLUM* L. (THYMI HERBA AND SERPYLLI HERBA) EU

Thymus vulgaris (known as garden or common thyme) and wild thyme (*T. serpyllum*, mother of thyme or serpyllum, Lamiaceae) are indigenous to Europe, especially the Mediterranean region, and are cultivated extensively. They are small, bushy herbs, with small, elliptical, greenish-grey, shortly stalked leaves. Those of thyme are up to about 6 mm long and 0.5–2 mm broad, with entiren recurved margins. The leaves of wild thyme are a little broader and the margins are not recurved; it has leaves with long trichomes at the base. Microscopically, the herbs are similar; both having the characteristic Lamiaceous glandular trichomes; the rather subtle differences are described in the Eur. Ph. Both have a characteristic odour of thymol and are used as culinary herbs.

Constituents

The active principle is the volatile oil, which has the major constituent thymol, with lesser amounts of carvacrol, 1,8-cineole, borneol, thymol methyl ether and α-pinene. However, the flavonoids (apigenin, luteolin, thymonin, etc.) and the polyphenolic acids (labiatic, rosmarinic and caffeic) are expected to contribute to the anti-inflammatory and antimicrobial effects.

Therapeutic uses and available evidence

Thyme, and oil of thyme, are carminative, antiseptic, antitussive, expectorant and spasmolytic, and, as such, are used for coughs, bronchitis, sinusitis, whooping cough and similar respiratory complaints. Most of the activity is thought to be due to the thymol, which is expectorant and highly antiseptic. Thymol and carvacrol are spasmolytic and the flavonoid fraction has a potent effect on

the smooth muscle of guinea pig trachea and ileum. Thymol (Fig. 24.1) is a popular ingredient of mouthwashes and dentifrices because of its antiseptic and deodorant properties. The oil may be taken internally in small doses of up to 0.3 ml, unless for use in a mouthwash, which is not intended to be swallowed in significant amounts.

Thymol is irritant, and toxic in overdose, and should be used with care.

SAGE, *SALVIA OFFICINALIS* L. (SALVIAE FOLIUM) AND *SALVIA* SPP. EU

Salvia officinalis L. (syn. garden or red sage, Lamiaceae) is indigenous to Europe, especially the Mediterranean region, and cultivated extensively. Spanish sage is *S. officinalis* subspp. *lavandulifolia* (Vahl) Gams; Greek sage is *S. triloba* L. fil. The leaves are stalked, 3–5 cm long and 1–2.5 cm broad, oblong or lanceolate and rounded at the base and at the apex. Sage has a strong, characteristic, odour. It is widely used as a culinary herb.

Constituents

Sage contains a volatile oil, with α- and β-thujone as the major components (usually about 50%), and cineole, borneol, camphor, 2-methyl-3-methylene-5-heptene and others. Spanish sage does not contain thujone; Greek sage contains only small amounts. Diterpene bitters picrosalvin (carnosol), carnosolic acid, abietane derivatives called royleanones, and flavonoids such as salvigenin, genkwanin, luteolin and derivatives are present, together with the polyphenolic acids salvianolic, rosmarinic and caffeic acids.

Therapeutic uses and available evidence

An infusion of sage is used as a gargle or mouthwash for pharyngitis, tonsillitis, sore gums, mouth ulcers and other similar disorders. Sage extracts and oil have been reported to be antimicrobial. The flavonoids and phenolic acid derivatives have antiviral and anti-inflammatory activity. Sage has a reputation for enhancing memory, and there is some clinical trial evidence (Scholey et al 2008), and the fact that it has anticholinesterase activity, to support this use.

SENEGA, *POLYGALA SENEGA* L. (POLYGALAE RADIX) EU

Senega (snake root, rattlesnake root, *Polygala senega* L., Polygalaceae) is native to the USA. In Chinese medicine, senega may also refer to *P. tenuifolia* Willd.; both species are used for similar purposes. The root is light yellowish-grey with a knotty crown, from which slender stems arise, bearing the remains of rudimentary leaves and buds at the base.

Constituents

The active constituents are triterpenoid saponins, the mixture generally known as 'senegin'. These are based on the aglycones presenegenin, senegenin, hydroxysenegin, polygalacic acid and senegnic acid, including the E- and Z-senegins II, III and IV, E- and Z-senegasaponins a, b and c, and others.

Therapeutic uses and available evidence

Senega is used primarily for chronic bronchitis, catarrh, asthma and croup. The saponins are the active constituents, as with other mucolytic plant drugs, and senega is usually taken orally as an infusion. The saponins also have immunopotentiating activity to protein and viral antigens, and exhibit less toxicity than quillaia saponins. They are anti-inflammatory and antiseptic. Senega extracts, the senegasaponins and the senegins are hypoglycaemic in rodents, the senegasaponins are inhibitors of alcohol absorption, and the senegins also have anticancer and anti-angiogenic effects *in vitro* (Arai et al 2011). The dose is usually equivalent to 0.5–1 g of the powdered root.

The saponins are irritant and haemolytic, but taken orally do not appear to pose many problems. Nausea and vomiting are the most common side effects and, in view of the other pharmacological actions, care should be taken with senega when given in high doses or to sensitive individuals.

IVY, *HEDERA HELIX* L. (HEDERAE FOLIUM) EU

Ivy is a saponin-containing expectorant. It is a common European plant, found also in northern and eastern Asia and introduced into America. *Hedera helix* (Araliaceae) has dark green leathery leaves, shiny, with 3–4 triangular lobes. The berries are small, purplish-black and globular, with the calyx ring visible at the apex. Both leaves

and berries may be used as part of phytotherapeutic preparations. The berries are somewhat toxic if consumed.

Constituents

The actives are saponins based on oleanolic acid, bayogenin and hederagenin, including the hederosaponins (or hederacosides) B, C and D, and α- and β-hederin, the polyyne falcarinol, and also flavonoids.

Therapeutic uses and available evidence

Ivy extracts are used in preparations for bronchitis and catarrh, as an expectorant. The saponins and sapogenins are the main active ingredients; they are expectorant and antifungal. Few clinical studies have been carried out, and further work is needed (Holzinger and Chenot 2011). One study showed that after 7 days of therapy with dried ivy leaf extract, 95% of patients showed improvement or healing of their symptoms, and it was safe and well-tolerated: the overall incidence of adverse events was 2.1%, mainly gastrointestinal disorders (Fazio et al 2009).

Both the saponin and the flavonoid fractions have spasmolytic effects.

A specific mode of action relevant for respiratory conditions of the saponins has been postulated: hederacoside C (which is converted into α-hederin by esterases) as well as its aglucone hederagenin, acts on G protein-linked β_2-adrenergic receptors of epithelial lung cells, resulting ultimately in an indirect β_2-sympathomimetic effect (Hegener 2004). Ivy extracts are often used in cosmetic preparations to treat cellulite, with some success. Ivy saponins are being widely investigated for their antileishmanial, molluscicidal, antimutagenic, antithrombin and anticlastogenic effects. The usual therapeutic dose as an expectorant is 0.3 g of crude drug, or equivalent.

Like all saponin-containing drugs, ivy can be irritant and allergenic. These effects are also due at least in part to the falcarinol content.

TOLU BALSAM, *MYROXYLON BALSAMUM* L. (BALSAMUM TOLUTANUM) EU

The resin, which is collected from incisions in the bark and sapwood of *Myroxylon balsamum* (Fabaceae), is a light brown, fragrant, balsamic resin, softening when warm and becoming brittle when cold. It has a pleasant, sweetish, aromatic, vanilla-like odour.

Constituents

The main constituents of the balsam are cinnamic and benzoic acids, their esters such as benzyl benzoate and cinnamyl cinnamate, and esters with resin alcohols, including coniferyl and hydroconiferyl benzoates.

Therapeutic uses and available evidence

Balsam of tolu is expectorant, stimulant and antiseptic. It is used in cough mixtures and pastilles, and as a lozenge base. Although there is no modern clinical evidence, many balsams are used for similar purposes and generally agreed to have a useful therapeutic role as expectorants, antiseptics and demulcents. Balsam of tolu is an ingredient in Friar's balsam, which is used as a steam inhalation and also as a protectant in skin formulations. The antimicrobial activity is due to the benzyl benzoate and benzyl cinnamate content.

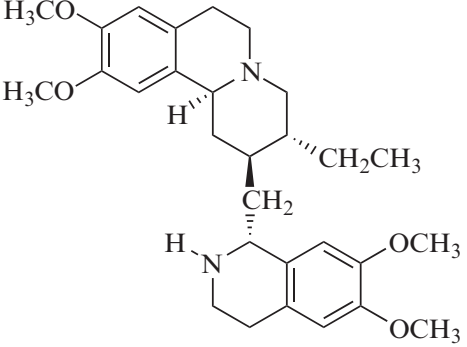
Tolu balsam, like many other balsam resins, can cause allergic reactions.

IPECACUANHA, *CEPHAELIS IPECACUANHA* A. RICH AND *C. ACUMINATA* KARSTEN (IPECACUANHAE RADIX) EU

'Ipecac' is obtained from the root and rhizome of *Cephaelis ipecacuanha* and C. *acuminata* (Rubiaceae). Rio, Matto Grosso and Brazilian ipecac are used to describe *C. ipecacuanha* (syn. *Psychotria ipecacuanha* Stokes) and Cartagena, Nicaragua or Panama ipecac, *C. acuminata.* They are native to tropical central and south America and cultivated in southern Asia. *C. ipecacuanha* root is slender, twisted and reddish brown, up to about 4 mm in diameter, with a characteristic ringed appearance. *C. acuminata* is larger, with fewer annulations. The root can be identified microscopically by the characteristic tracheids and bordered pitted xylem vessels, and the needle crystals of calcium oxalate (see Eur. Ph.).

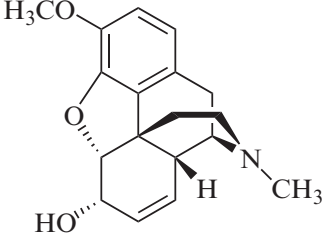
Constituents

Both species contain isoquinoline alkaloids as the active principles, usually about 2–3%. The most important are emetine (Fig. 16.6) and cephaeline, with psychotrine and some others.



Emetine

Fig. 16.6



Codeine

Fig. 16.7

Therapeutic uses and available evidence

Ipecac extract is an ingredient of many cough preparations, both elixirs and pastilles, because of its expectorant activity. It is also well known as an emetic and has been employed to induce vomiting in cases of drug overdose, particularly in children. This use is, however, highly controversial (Quang and Woolf 2000). The alkaloids are amoebicidal, but the emetic activity means that they are rarely used for this purpose. There is little clinical evidence for the use of ipecac as an expectorant but it has a long history of traditional use. Ipecacuanha Liquid Extract BP is given at a dose of 0.25–1 ml.

Ipecac causes vomiting in large doses and the alkaloids are cytotoxic.

COUGH SUPPRESSANTS

Cough is a reflex action and a symptom of other diseases such as asthma and colds due to 'nasal drip'. Cough suppressants may be useful in some instances, but efficacy is not fully proven and if expectoration is required, for example to avoid sputum retention, they should not be used. They are not recommended for small children who are highly susceptible to respiratory depression caused by opiates. Codeine and semi-synthetic opiates such as dextromethorphan are the most common antitussives; in severe cases such as in lung cancer, stronger opiates such as methadone may be used.

CODEINE EU

Although found in opium (*Papaver somniferum*), codeine (Fig. 16.7) is usually used as the isolated alkaloid, in the form of a salt (usually phosphate) formulated as a linctus, at a dose of 5–10 mg 4-hourly, to treat cough. The dose for treating diarrhoea and pain is much higher (up to 240 mg daily in divided doses).

Codeine is sedating and constipating. In large doses it may cause respiratory depression and should not be used in hepatic or renal impairment. It is also liable to abuse and is available only on prescription in many countries.

GENERAL PHYTOMEDICINES USED IN COLDS AND INFLUENZA

Some of these herbs have antiviral and anti-inflammatory activity, some are demulcents or stimulate the immune system, and many have several of these properties. They are often used in combination with other ingredients as herbal teas for the supportive or symptomatic therapy of respiratory disease.

DEMULCENTS AND EMOLLIENTS

Many herbal teas, made particularly from flowers and leaves, are used to obtain symptomatic relief from colds and influenza. Some are diaphoretic (induce sweating), some are anti-inflammatory and analgesic, others are mucilagenous and soothing, and many have some antiviral activity due to the polyphenolic constituents. They are used as a general supportive measure and are usually pleasant to take. As well as the plants discussed here, other botanical drugs rich in mucilage are also used for respiratory conditions, for example the lichen 'Icelandic Moss' from *Cetraria islandica* (L.) Ach. (Parmeliaceae).

COLTSFOOT, *TUSSILAGO FARFARA* L. (TUSSILAGO FOLIUM) EU

Coltsfoot (Asteraceae) is a common wild plant in Britain and Europe, growing in damp places. The flowers appear in early spring before the leaves. The leaves are hoof-shaped, with angular teeth on the margins, green above and coated with matted, long white hairs on the lower surface. The flowers are bright yellow, with a characteristic scaly pedicel. Both the leaves and flowers are used medicinally.

Constituents

The main constituent is a mucilage composed of acidic polysaccharides, together with flavonoids, triterpenes and sterols. Pyrrolizidine alkaloids, including senkirkine, tussilagine and isotussilagine, may be present in variable amounts, usually very minor (about 0.015%) or absent, depending on source.

Therapeutic uses and available evidence

Coltsfoot is used for pulmonary complaints, irritating or spasmodic coughs, whooping cough, bronchitis, laryngitis and asthma. The polysaccharides are anti-inflammatory and immunostimulating, as well as demulcent, and the flavonoids also have anti-inflammatory and antispasmodic action.

The pyrrolizidine alkaloids are known to cause hepatotoxicity in rats fed daily on high doses, but not on daily low-dose regimens, and appear not to cause damage to human chromosomes *in vitro*. However, samples containing significant quantities of these alkaloids should not be used.

ELDERFLOWER AND ELDERBERRY (FRUIT), *SAMBUCUS NIGRA* L. (SAMBUCI FLOS, SAMBUCI FRUCTUS) EU

Sambucus nigra (Adoxaceae or Sambucaceae), the Black or European elder (berry), is a common European hedge tree or shrub. The flowers appear in May as small, creamy-white, flat-topped umbel-like clusters and are followed by small, shiny, purplish-black berries. Most parts of the plant are used, but most commonly the flowers and berries, which are also used to make refreshing drinks and country-style wines. The berries should not be eaten raw as they contain lectins, which can cause gastrointestinal disturbances, but which are destroyed by heat. Related species are toxic (e.g. Danewort, *S. ebulus*).

Constituents

Triterpenes including ursolic and oleanolic acid derivatives, flavonoids (rutin, quercetin, nicotoflorin, hyperoside), and phenolic acids such as chlorogenic acid are the main actives. The flowers contain an essential oil.

Therapeutic uses and available evidence

Elder flowers are used as an infusion or herbal tea, and a mixture with peppermint is a traditional remedy for colds and influenza. They induce perspiration, which is thought to be beneficial in such cases. Recent studies show an *in vitro* activity against several strains of influenza virus, and a clinical study has also demonstrated a reduction in the duration of flu symptoms for the berries (see Vlachojannis et al 2010 for review). The effect was attributed to an increase in inflammatory cytokine production as well as a direct antiviral action. The usual dose is about 3 g of flowers infused with 150 ml of hot water, but is not critical. Elder flowers are non-toxic and no side effects have been reported. Both the berries and the flowers are used to make cordials which are taken medicinally for their reputed antioxidant and antiviral properties.

LINDEN FLOWERS, *TILIA* SPP. (TILIAE FLOS) EU

Linden flowers (although called 'lime flowers' they are not related to lime fruit) are from *Tilia platyphylla* Scop., *T. cordata* Mill. and their hybrid (Tiliaceae). They are ornamental trees native to Europe. The pedicel bears 3–6 yellowish-white, five-petalled, fragrant flowers on stalks half-joined to an oblong bract.

Constituents

The flowers contain volatile oil (linalool, germacrene, geraniol, 1,8-cineole, 2-phenyl ethanol and others), flavonoids (hesperidin, quercetin, astralagin, tiliroside), a mucilage of arabinose, galactose and rhamnose polysaccharides, polyphenolics such as chlorogenic and caffeic acids, and GABA (γ-aminobenzoic acid).

Therapeutic uses and available evidence

Linden flowers are used for feverish colds, catarrh, coughs and influenza. They are used as herbal teas to induce diaphoresis (perspiration) like elder and

at a similar dose (see above). The polysaccharides are soothing and adhere to epithelial tissue, producing a demulcent effect. The other main use of the flowers is for nervous disorders; the extract is thought to act as an agonist for the peripheral benzodiazepine receptor. There is evidence that components of the aqueous extract of the flowers bind to GABA receptors in rat brain (an effect not due entirely to the GABA content of the extract) and mild sedative effects were confirmed using the elevated maze anxiety test in mice (Anesini 1999). Linden flowers are non-toxic and no side effects have been reported.

MALLOW FLOWER AND LEAVES, *MALVA SYLVESTRIS* L. (MALVAE FLOS AND MALVAE FOLIUM) EU

The common mallow (*Malva sylvestris* L., Malvaceae) is a wild plant indigenous to southern Europe but naturalized worldwide. The leaves are downy, with 5–7 lobes, and prominent veins on the under surface. The flowers are mauve, with darker veins; both are used for their mucilage content.

Constituents

The main constituents are mucilages, sulphated flavonol glycosides such as gossypin-3-sulphate, hypolaetinglucoside-3′-sulphate and others, and anthocyanins (malvin, the diglucoside of malvidin, and delphinidin).

Therapeutic uses and available evidence

Mallow is a demulcent and pectoral. An infusion is used for colds and coughs, and the mucilage from the leaves is anti-inflammatory with anticomplement activity. Little clinical evidence is available but there is a long tradition of historical use. No adverse effects are known.

MARSHMALLOW LEAF AND ROOT, *ALTHEA OFFICINALIS* L. (ALTHAEAE FOLIUM, ALTHAEAE RADIX) EU

Both the leaves and the rootstock of the marshmallow (Malvaceae) are used as a demulcent, expectorant and emollient. The plant is a downy perennial reaching up to 2 m in height with leaves broadly ovate or cordate, 10–20 cm long and about 10 cm wide, with 3–7 rounded lobes, palmate veins and a crenate margin. The flowers are pink, five-petalled, up to 3 cm in diameter. The root as it appears in commerce is dried, fibrous, cream-white when peeled, deeply furrowed longitudinally and with some root scars. It is largely tasteless.

Constituents

Both rootstock and leaves are rich in mucilage, consisting of a number of polysaccharides (composed of L-rhamnose, D-galactose, D-galacturonic acid and D-glucuronic acid) and others. It also contains common flavonoids, especially derivatives of kaempferol and quercetin.

Therapeutic uses and available evidence

Both the leaves and root are used internally for coughs and bronchial complaints. Extracts of both are used occasionally for gastric and urinary inflammation in general, and for cystitis. They may be applied externally as a soothing poultice and vulnerary. The mucilages have proven biological activity, including the stimulation of phagocytosis *in vitro.* Antimicrobial and anti-inflammatory activities have also been documented. Several of the polysaccharides isolated from the roots have been found to have antitussive activity. The most common use of extracts of marshmallow root is in the making of confectionery.

PELARGONIUM, *PELARGONIUM SIDOIDES* DC AND *P. RENIFORME* CURT (PELARGONII RADIX) EU

Pelargonium is obtained from two southern African species, *Pelargonium sidoides* and *P. reniforme* (Geraniaceae) where the tubers, stems and root have been used for centuries to treat a range of infectious conditions.

Constituents

The main active components are hydrolysable tannins, (+)-catechin, gallic acid and methyl gallate, including a unique series of O-galloyl-C-glucosylflavones. Flavonoids including myricetin and quercetin-3-O-beta-d-glucoside, coumarins including scopoletin,

umckalin, 5,6,7-trimethoxycoumarin and 6,8-dihydroxy-5,7-dimethoxycoumarin, are present in both species. A series of benzopyranones has been isolated from *P. sidiodes*, and the pelargoniins (a type of ellagitannin) and a diterpene, reniformin, have been found in *P. reniforme*.

Therapeutic uses and available evidence

In Germany, a standardized extract of *Pelargonium sidoides* (EPs® 7630, also known as Umckaloabo®) is registered by the Federal Institute for Drugs and Medical Devices (BfArM) for the indication 'acute bronchitis' and several randomized, double-blind, placebo-controlled clinical trials support its efficacy in adults and children (Agbabiaka et al 2008). The extract EPs® 7630 has multiple effects which are beneficial in respiratory infections, and include antiviral, antibacterial, immunomodulatory and cytoprotective effects. It also increases the frequency of ciliary beats, thus helping to remove pathogens for the upper respiratory tract, and inhibits the interaction between bacteria and host cells. A recent study has found that EPs® 7630 interferes with the replication of different respiratory viruses including seasonal influenza A virus strains, RSV, human coronavirus, parainfluenza virus and coxsackie virus (Michaelis et al 2011). This extract is also given to athletes to help strengthen the immune system, which can be compromised by extreme exercise, to protect against colds. A study in athletes submitted to intense physical activity found that *Pelargonium sidioides* increased the production of secretory immunoglobulin A in saliva, and decreased levels of both interleukin-15 and interleukin-6 in serum, suggesting a strong modulating influence on the immune response associated with the upper airway mucosa (Luna et al 2011).

IMMUNOSTIMULANTS

Immune stimulation is usually measured using parameters such as an increase in numbers of circulating immune cells, or enhanced phagocytosis after inoculation with a pathogen. It is notoriously difficult to substantiate claims for the prevention of disease, since very large clinical studies are needed for statistical validity, and these are difficult and expensive to perform. However, echinacea is taken widely and the use of an Oriental herb, astragalus, is increasing in the West for the same indications.

ECHINACEA, *ECHINACEA PALLIDA* (NUTT.) BRITT., *E. PURPUREA* MOENCH AND *E. ANGUSTIFOLIA* (DC.) HELL. (ECHINACEAE HERBA, RADIX) EU

Members of the genus *Echinacea* (Asteraceae) are widely distributed in North America and have a long tradition of use, both by the American Indians and the settlers, who developed the first commercial preparations during the 19th century. Both aerial parts and secondary roots are used. The indigenous people used *E. pallida* in particular for a variety of illnesses, such as pain, inflammatory skin conditions and toothache. The three botanical species are used in the preparation of phytomedicines to 'prevent colds and other respiratory infections', as immunostimulants. The complex situation regarding species, quality of products made from them and method of production makes an assessment of the clinical efficacy very difficult. Echinacea is often combined with garlic, for the treatment of colds and allergic rhinitis.

Constituents

Numerous compounds have been identified, but the most pharmacologically relevant ones are not known. All species contain similar types of compounds, although not necessarily the same individual ones. The most important are the caffeic acid derivatives, including echinacoside (Fig. 16.8) (*E. pallida* root), cichoric acid (*E. purpurea* aerial parts) and others, and the alkylamides (found throughout the plant in all three species), which are a complex mixture of unsaturated fatty acid derivatives. Some have a diene or diyne structure (with two unsaturated and two triple unsaturated groups) or a tetraene structure (with four unsaturated groups) linked via an esteramide to a (2)-methylpropane or (2)-methylbutane residue.

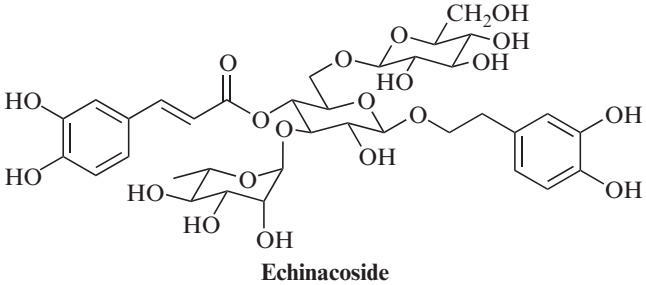


Fig. 16.8

Therapeutic uses and available evidence

Echinacea preparations are available both as traditional herbal medicinal products used to relieve the symptoms of the common cold and influenza type infections, but also as preparations with a well-established use. There is some evidence in the treatment and prevention of respiratory infections, but more limited evidence for slow healing wounds using topical applications. Clinical evidence for uses as an immunostimulant is available for some of the chemically characterised extracts. Overall a series of meta-analyses showed that Echinacea preparations *seem to be* efficacious both therapeutically (reducing symptoms and duration) and in terms of prophylaxis against the common cold (Shah et al 2007, Woelkart et al 2008). However, *Echinacea* preparations tested in clinical trials differ greatly. There is better evidence that preparations based on the aerial parts of *E. purpurea* might be effective for the early treatment of colds in adults but the results are not fully consistent. A mechanism of action has been postulated by Chicca et al (2009), suggesting that the alkylamides dodeca-2 *E*,4*E*,8*Z*,10*Z*-tetraenoic acid isobutylamide (A1) and dodeca-2*E*, 4*E*-dienoic acid isobutylamide (A2) bind to the cannabinoid-2-(CB2) receptor and are the main anti-inflammatory and immune-modulatory principles, acting in synergy. In addition, alkylamides potently inhibit LPS-induced inflammation in human whole blood and exert modulatory effects on cytokine expression, but these effects are not exclusively related to CB2 binding.

Echinacea appears to be safe, although allergic reactions have been reported. The risk of interactions seems to be very limited (Modarai et al 2007).

ASTRAGALUS, *ASTRAGALUS MEMBRANACEUS* (FISCH.) BGE. (ASTRAGALI RADIX) EU

Astragalus membranaceus (Fabaceae) is an herbaceous perennial native to north-eastern China, central Mongolia and Siberia. The drug is known in Chinese medicine as Huang qi. The use of *Astragalus* root as a general tonic dates back to the legendary Chinese emperor Shen-Nong. The root consists of a long cylindrical tap root, which is internally yellowish in colour, but rootlets should be absent.

Constituents

Triterpenoid saponins, the astragalosides I–VIII, and their acetyl derivatives, agroastragalosides I–IV, astramembranins I and II and others; isoflavones including formononetin and kumatakenin, and polysaccharides known as astrogaloglucans.

Therapeutic uses and available evidence

A number of clinical studies, supported by data from over 1000 patients in China, confirm the use of astragalus as an immunostimulant for use in colds and upper respiratory infections. It is also used prophylactically. In China it is also used as an adjunctive in the treatment of cancer, and appears to potentiate the effects of interferon. It also has antioxidant, hepatoprotective and antiviral activity and is used to enhance cardiovascular function (www.thorne.com 2003). Many animal studies have been carried out, but specific data on toxicity are sparse. In general, astragalus is well tolerated but should probably be avoided in autoimmune diseases.

ANDROGRAPHIS, *ANDROGRAPHIS PANICULATA* (BURM.F.) WALL. EX NEES (ANDROGRAPHIS PANICULATAE HERBA)

Andrographis paniculata (Acanthaceae), also known as 'green chiretta', is an erect annual herb found in north-eastern India and many parts of Asia. It is extremely bitter in taste and has been referred to as the 'king of bitters'. It is an important herb in Ayurveda where it is known as kalmegh.

Constituents

The main actives are diterpenes, known as andrographolides, and consist of andrographolide and its many analogues, including neoandrographolide, isoandrographolide, 14-deoxyandrographolide, 14-deoxy-14,15-dehydroandrographolide, 3,19-isopropylideneandrographolide and 14-acetylandrographolide and many others. Flavonoids and polyphenols such as 7-O-methylwogonin, apigenin, onysilin and 3,4-dicaffeoylquinic acid are also present. An alkaloid, andrographine, and a series of sesquiterpene lactones, paniculides A, B, and C, are also present in the root.

Therapeutic uses and available evidence

Andrographis is most commonly used as an immune stimulant, but is also reputed to possess antihepatotoxic, antimicrobial, antithrombogenic, antiinflammatory and anticancer properties (www.thorne.com 2003). Andrographolide has been shown to have immunostimulatory activity, shown by an increase in proliferation of lymphocytes and production of interleukin-2, and the antiinflammatory activity has been demonstrated by an inhibition of NFB, nitric oxide, PGE2, IL-1β, IL-6, LTB4, TXB2 and histamine (Bao et al 2009, Chandrasekaran et al 2010). In one Chilean study, andrographis herb had a significant drying effect on the nasal secretions of cold sufferers who took 1,200 mg of the extract daily for 5 days (Cáceres et al 1999). A systematic review of the literature has suggested the herb alone (or in combination with Eleutherococcus) may be an appropriate treatment for uncomplicated acute upper respiratory tract infection (Poolsup et al 2004).

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The central nervous system

Drugs acting on the central nervous system (CNS) include the centrally acting (mainly opioid) analgesics, anti-epileptics and anti-Parkinson agents, as well as those for psychiatric disorders. Drugs of plant origin are important in all these areas, although not usually for self-medication. They are also of historical interest; for example, the antipsychotic drug reserpine, isolated from *Rauvolfia* species, revolutionized the treatment of schizophrenia and enabled many patients to avoid hospitalization before the introduction of the phenothiazines (such as chlorpromazine) and the newer atypical antipsychotics (olanzapine and risperidone). Unfortunately, reserpine depletes neurotransmitter levels in the brain (it is used as a pharmacological tool in neuroscience for this reason) and so can cause severe depression, and it has recently been implicated in the development of breast cancer. There are no other currently useful antipsychotics obtained from plants and they will not be covered here. Similarly, the useful anti-epileptics are synthetic, with the possible exception of the cannabinoids, from *Cannabis sativa*, which are currently under investigation.

However, for milder psychiatric conditions, phytotherapy can provide useful support. The prevalence of mental health problems, particularly depression and anxiety, in the general population is around one in six people, and around 40% of people with mental health problems will have symptoms of both anxiety and depression. Depression is more common in women than men; around one-half of women and one-quarter of men will be affected by depression at some time. However, other than in mild cases, these disorders are not suitable for self-treatment, and medical supervision is necessary. Sleep disturbances, such as insomnia and early morning awakening, are characteristic of depression and anxiety, although they can also occur independently of mental health problems. Around one-third of adults are thought to experience insomnia, and most do not seek treatment from a physician. Phytotherapy has a role to play in helping to re-establish a regular pattern of sleep. Valerian (Fig. 17.1), for example, has been advocated as a means of alleviating the symptoms of benzodiazepine withdrawal.

Migraine is a common disorder, but can be debilitating. Opioid analgesics are used, and the synthetic 5-HT_1 (5-hydroxytryptamine) antagonists (sumatriptan, rizatriptan) are highly effective, although they are not used for the prophylaxis of migraine. Ergotamine is a potent drug used as a last resort in attacks of migraine. Feverfew is sometimes used to prevent attacks, and will be discussed briefly.

In cases of dementia and Alzheimer's disease, natural compounds have played a key role in their symptomatic treatment. Galantamine (from the snowdrop, *Galanthus nivalis*) and derivatives of physostigmine (e.g. rivastigmine) are clinically used as cholinesterase inhibitors. Some plant extracts, such as sage and rosemary, have similar but milder effects and are being investigated for memory improvement. *Ginkgo biloba* has cognition-enhancing properties and can be used for mild forms of dementia.

HYPNOTICS AND SEDATIVES

The difference between a sedative and hypnotic is generally a question of dose. Plant products used in this way are not as potent as synthetic drugs, but neither do they have many of the disadvantages.

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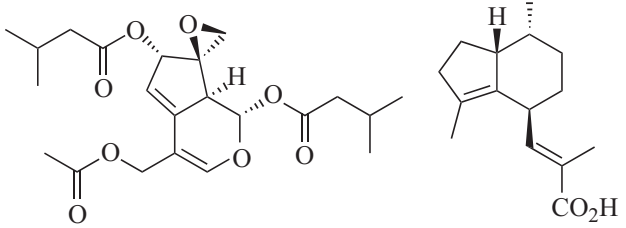


Fig. 17.1

However, as with synthetic hypnotics, these medicines are generally intended for short-term use.

HOPS, *HUMULUS LUPULUS* L. (HUMULI LUPULI STROBULI) EU

Humulus lupulus (Cannabaceae), often referred to by its common name of hops, has been used traditionally for insomnia, neuralgia and excitability. It is cultivated in several European countries, including England, France and Germany. The part of the plant used pharmaceutically is the female flower heads (known as 'strobiles'). These are composed of overlapping bracts, which enclose the ovary. Hops have a characteristic odour.

Constituents

The main active constituents of hops are the bitter principles found in the oleo-resin. These include the α-acid humulone and the β-acid lupulone, and their degradation products, such as 2-methyl-3-buten-2-ol (Fig. 17.2). Other constituents include flavonoids, chalcones, tannins and volatile oils.

Therapeutic uses and available evidence

Modern pharmaceutical uses of hops include sleep disturbances and restlessness. Sedative and hypnotic activities have been documented *in vivo* (mice) for extract of hops, and for the bitter acid degradation product 2-methyl-3-buten-2-ol. Clinical studies provide some evidence of the hypnotic effects of hops given in combination with the herbal sedative,

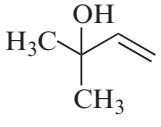


Fig. 17.2

hypnotic valerian (Zanoli and Zavatti 2008). Antibacterial and antifungal activities have been documented in vitro for certain constituents of hops. Hops are non-toxic, as their use in beer would suggest. Cheers!

LEMON BALM, *MELISSA OFFICINALIS* L. (MELISSAE FOLIUM) EU

Melissa officinalis L. (syn. 'balm' and 'sweet balm', Lamiaceae) has been used traditionally for its sedative effects, as well as for gastrointestinal disorders. The dried leaves are the parts used pharmaceutically. The herb is described in Chapter 17.

Constituents

The volatile oil of melissa contains numerous constituents, mainly monoterpenes, particularly aldehydes (e.g. as citronellal, geranial and neral) and sesquiterpenes (e.g. β-caryophyllene). Flavonoids, including quercetin, apigenin and kaempferol, and polyphenols (e.g. hydroxycinnamic acid derivatives) are also present in the herb. Melissa is listed in the Eur. Ph, which states that the drug contains not less than 4.0% of total hydroxycinnamic derivatives, expressed as rosmarinic acid, calculated with reference to the dried drug.

Therapeutic uses and available evidence

Sedative and antispasmodic effects have been documented for melissa extracts using *in vivo* studies (mice, rats). It is used for nervous or sleeping disorders and functional gastrointestinal complaints. There has been no clinical investigation of the sedative effects of melissa alone in individuals with sleeping disorders. However, clinical trials have explored the effects of melissa in combination with other herbal sedatives (e. g. valerian and hops) and provide some evidence to support the sedative and hypnotic effects of such preparations. Antihormonal effects of balm, mainly antithyroid, have been documented and, recently, cholinergic activity has been found for extracts using human cerebral cortical cell membrane homogenates. Dried lemon balm is usually taken internally in the form of a herbal tea, at a dose of 2–4 g three times a day. Melissa extracts are also applied topically in cases of *Herpes simplex labialis* resulting from HSV-1 infection (see antiinfectives). Lemon balm is regarded as non-toxic, although it should not be used to excess because

of the reputed antithyroid activity. For review, see Ulbricht et al 2005.

KAVA, *PIPER METHYSTICUM* FORST. (PIPERIS METHYSTICI RHIZOME)

Piper methysticum (Piperaceae), also known as kava-kava or kawa, has been used in the Pacific Islands, notably Fiji, for hundreds of years. It is a small shrub with heart-shaped leaves and thick, woody roots and rhizomes, which are ground or chewed to release the actives. These are then fermented to make the ceremonial drink Kava, which induces a relaxed sociable state, and is given to visiting dignitaries (including the Pope and the Queen of England). Kava is used medicinally for its tranquillizing properties and numerous other disparate complaints. Recent safety concerns have resulted in Kava products being withdrawn from sale at present (2011), but moves are being made to try to re-introduce it into the EU (Sarris et al 2011).

Constituents

The main components of kava are the kavalactones (also known as kavapyrones), including kavain, dihydrokavain, methysticin, yangonin and desmethoxyyangonin.

Therapeutic uses and available evidence

In vitro studies have previously provided some conflicting data on receptor interactions of kava extract and isolated kavalactones. Current thinking is that kavalactones potentiate $GABA_A$ receptor activity. Other receptor binding studies demonstrate no interaction with benzodiazepine receptors. The efficacy of kava extracts in relieving anxiety is supported by data from several randomized, placebo-controlled, clinical trials, for example an aqueous kava preparation produced significant anxiolytic and antidepressant activity and appeared equally effective in cases where anxiety is accompanied by depression (Sarris et al 2009). Overall, studies indicate reductions in anxiety after 4–12 weeks of treatment with kava extracts at dosages equivalent to 60–240 mg of kavalactones daily.

Kava extracts are generally well tolerated when used at recommended doses for limited periods. However, kava-induced liver injury has been demonstrated in several patients worldwide, and it has been suggested that this is due to inappropriate quality of the kava raw material (Teschke et al 2011). There may also be a pharmacogenomic component to the toxicity (Sarris et al 2011) and assessment of the causal role of kava is complicated by other factors, including concomitant drugs linked with liver toxicity, and alcohol. There is circumstantial evidence for the roles of toxic metabolites, inhibition of cyclooxygenase (COX) enzymes and depletion of liver glutathione, and pharmacogenomic effects are likely, particularly for cytochrome P450 genes. Experimental and clinical cases of hepatotoxicity show evidence of hepatitis, but the question remains whether this inflammation is caused by components of kava directly, or is due to downstream effects (Zhang et al 2011). A recent study in hepatocytes has shown that kavain has minimal cytotoxicity and methysticin moderate concentration-dependent toxicity, whereas yangonin displayed marked toxicity (Tang et al 2011).

PASSION FLOWER, *PASSIFLORA INCARNATA* L. (PASSIFLORAE HERBA) EU

Passion flower (*Passiflora incarnata* L., Passifloraceae) is also known by the common names passion vine, maypop and others. The plant is a climbing vine, native to South America, but now also grown widely including in the USA and India. The dried leafy aerial parts, which normally include the flowers and fruits, are used pharmaceutically. The flower shows a distinctive shape of a cross, and gives the name passion (which refers to Christian connotations rather than romantic). There are numerous curling tendrils and the leaves are three-lobed. The active constituents have not yet been clearly established. The edible passion fruit is from *P. edulis*.

Constituents

The active constituents are not known, but the flavonoids are thought to be important, particularly chrysin and related compounds. These include schaftoside, isoschaftoside, orientin, homoorientin, vitexin, isovitexin, kaempferol, luteolin, quercetin, rutin, saponaretin and saponarin. Alkaloids of the harman type are present in low amounts (the presence of harmine, harmaline, harmol and harmalol has been disputed) as well as β-carbolines. *P. edulis* contains similar types of compounds and cycloartane triterpenoids such as the cyclopassifloic acids and cyclopassiflosides. Passion flower is included in the Eur. Ph. The drug should contain not less

than 1.5% of total flavonoids, expressed as vitexin, assayed by a colorimetric method.

Therapeutic uses and available evidence

The historical medicinal uses of passion flower include treatment of insomnia, hysteria, nervous tachycardia and neuralgia. Modern pharmaceutical uses include nervous restlessness and insomnia due to nervous tension, and, specifically based on the THMPD, for the temporary relief of symptoms associated with stress and of mild anxiety.

Animal studies (mice, rats) have documented CNS-sedative effects or reductions in motility for aqueous ethanolic extracts of passion flower and for the constituents maltol and ethylmaltol. Anxiolytic activity has been reported in mice (Sampath et al 2010) and modulation of the GABA system is known to be involved (Appel et al 2010, Elsas et al 2010). Sedative effects are attributed at least in part to the flavonoid, particularly chrysin, content. There are few clinical studies of passiflora; however, a preliminary double-blind randomized trial using 36 patients with generalized anxiety showed the extract to be as effective as oxazepam, but with a lower incidence of impairment of job performance. It has been advocated as an adjunctive therapy for opiate withdrawal symptoms (for review, Miyasaka et al 2007). Generally, passiflora is well tolerated with few side effects; however, isolated reactions involving nausea and tachycardia in one case, and vasculitis in another, have been reported.

VALERIAN, *VALERIANA OFFICINALIS* L. (VALERIANAE RADIX) EU

Valeriana officinalis (Valerianaceae), commonly known as valerian, all-heal, and by many other vernacular (common) names, is among the most well documented of all medicinal plants, particularly in northern Europe. It is an herbaceous plant, reaching about 1 m in height, and is cultivated in many European countries, as well as in Japan and North America. Valerian has a long history of traditional use. Historically, it was used in the treatment of conditions involving nervous excitability, such as hysterical states and hypochondriasis, as well as in insomnia. The parts used pharmaceutically are the root, rhizomes and stolons, which are yellowish grey to pale greyish-brown. The rhizomes may be up to 50 mm long and 30 mm in diameter, whereas the roots may be around 100 mm long and 1–3 mm in diameter. Valerian root has a characteristic smell, which is usually described as unpleasant.

Constituents

The main components of valerian are the volatile oil and the iridoid valepotriate constituents. The volatile oil contains monoterpenes and sesquiterpenes, such as β-bisabolene, caryophyllene, valeranone, valerianol, valerenol, valerenal, valerenic acid and derivatives (Fig. 17.1). The valepotriate compounds include valtrate, didrovaltrate and isovaltrate. The valepotriates readily decompose on storage and processing to form mainly baldrinal and homobaldrinal, which are also unstable. Valerian also contains alkaloids, including valerianine and valerine, and amino acids such as arginine, γ-aminobutyric acid (GABA), glutamine and tyrosine.

Valerian root is listed in the Eur. Ph., which requires that it contains not less than 5 ml/kg volatile oil for the whole drug, and not less than 3 ml/kg for the cut drug, calculated with reference to the dried drug. It should also contain not less than 0.17% of sesquiterpenic acids, expressed as valerenic acid.

Therapeutic uses and available evidence

In Europe valerian and its various preparations (tablets, tinctures) have been approved for the temporary relief of symptoms of mild anxiety and to aid sleep, and are generally based on traditional use. The sedative effects of valerian root are well documented. *In vivo* studies (in mice) have demonstrated CNS-depressant activity for the volatile oil, the valepotriates and the valepotriate degradation products. The sedative effects of valerian root are thought to be due to the activities of these different components, particularly valerenal and valerenic acid (constituents of the volatile oil), and the valepotriate compounds. Therefore, the profile of these constituents, and their concentrations, in a specific valerian preparation will determine its activity. Biochemical studies have indicated that certain components of valerian, particularly valerenic acid, may lead to increased concentrations of the inhibitory neurotransmitter GABA in the brain by inhibiting its catabolism, inhibiting uptake and/or by inducing GABA release. Increased GABA concentrations are associated with decreased CNS activity, which may, at least partly, explain valerian's sedative activity. It is not clear whether

valerian root extracts have effects on the binding of benzodiazepines to receptors. Modern medicinal uses for valerian root preparations are for insomnia, stress and anxiety. Clinical trials have tested the effects of valerian preparations on subjective (e.g. sleep quality) and objective (e.g. sleep structure) sleep parameters, and on measures of stress. Some, but not all, of these studies provide evidence to support the traditional uses of valerian. Several preparations contain valerian root in combination with other herbs reputed to have hypnotic and/or sedative effects, such as hops (*Humulus lupulus*) and melissa (*Melissa officinalis*) (see Salter and Brownie 2010 for review). It is recommended that valerian preparations should not be taken for up to 2 hours before driving a car or operating machinery; also, the effect of valerian preparations may be enhanced by alcohol consumption. There are isolated reports of hepatotoxicity associated with valerian-containing products, although causality has not been established.

ANTIDEPRESSANTS

ST JOHN'S WORT, *HYPERICUM PERFORATUM* L. (HYPERICI HERBA) EU

St John's wort (Hypericaceae) has a history of medicinal use, particularly as a 'nerve tonic' and in the treatment of nervous disorders. It is commonly used to treat mild and moderate forms of depression and is registered in the UK for the treatment of 'slightly low mood and mild anxiety'.

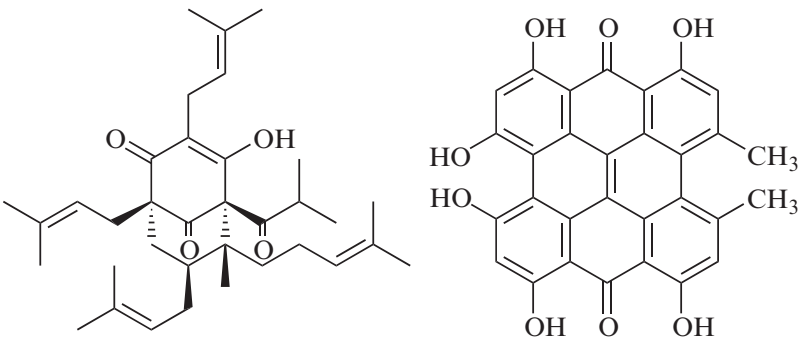
It is an herbaceous perennial plant native to Europe and Asia. The name St John's wort may have arisen as the flowers bloom in late June around St John's day (24 June). Herbal products containing St John's wort have been among the top-selling herbal preparations in developed countries in recent years. The dried herb (consisting mainly of the flowering tops, including leaves, unopened buds and flowers) is the part used pharmaceutically.

Constituents

St John's wort contains a series of naphthodianthrones, which include hypericin and pseudohypericin, and the prenylated phloroglucinols, such as hyperforin and adhyperforin. Initially, hypericin was considered to be the antidepressant constituent of St John's wort, although evidence has now emerged that hyperforin (Fig. 17.3) is also a major constituent required for antidepressant activity. Further research is necessary to determine which other constituents contribute to the antidepressant effect. The Eur. Ph. states that the drug should contain not less than 0.08% of total hypericins, expressed as hypericin, calculated with reference to the dried drug. Most products containing standardized extracts of St John's wort are still standardized on hypericin content, as hyperforin is fairly unstable. St John's wort also contains other biologically active constituents, such as flavonoids. The leaves and flowers also contain an essential oil, of which the major components are β-caryophyllene, caryophyllene oxide spathulenol, tetradecanol, viridiflorol, α- and β-pinene, and α- and β-selinene.

Therapeutic uses and available evidence

The precise mechanism of action for the antidepressant effect of St John's wort is unclear. Results of biochemical and pharmacological studies have



Hyperforin **Hypericin**

Fig. 17.3

suggested that St John's wort extracts inhibit synaptosomal uptake of the neurotransmitters, serotonin (5-hydroxytryptamine, 5-HT), dopamine and noradrenaline (norepinephrine) and GABA. Studies involving small numbers of healthy male volunteers have indicated that St John's wort extracts may have dopaminergic activity and effects on cortisol, which may influence concentrations of certain neurotransmitters. Previous *in vitro* studies suggested that St John's wort inhibited monoamine oxidase, although other studies failed to confirm this. Experimental studies involving animal models of depression provide supporting evidence for the antidepressant effects of St John's wort. Evidence from randomized controlled trials indicates that preparations of St John's wort extracts are more effective than placebo, and possibly as effective as conventional antidepressants, in the treatment of mild to moderate depression (for overview, see Linde 2009, Nahrstedt and Butterweck 2010). Generally, a few weeks' treatment is required before marked improvement is seen. St John's wort is not recommended for the treatment of major depression.

Standardized extracts of St John's wort are generally well tolerated when used at recommended doses for up to 12 weeks. Adverse effects reported are usually mild, and include gastrointestinal symptoms, dizziness, confusion and tiredness and, rarely, photosensitivity (due to the hypericin content). However, clinical trials of St John's wort suggest a more favourable short-term safety profile than some conventional antidepressants. Concern has been raised over interactions between St John's wort preparations and certain prescribed medicines, including anticonvulsants, cyclosporin, digoxin, HIV protease inhibitors, oral contraceptives, selective serotonin reuptake inhibitors, theophylline, triptans and warfarin. Patients taking these medicines should stop taking St John's wort and seek medical advice (except in the case of oral contraceptives) as dose adjustment of the prescribed medicines concerned may be necessary. St John's wort should not be used during pregnancy and lactation.

STIMULANTS

CNS stimulants are now rarely employed therapeutically, with the exception of caffeine, although they were important in the treatment of barbiturate poisoning (e.g. picrotoxin) or as a tonic (strychnine). Cola nut extract is used in many herbal tonics and, of course, in the ubiquitous soft drink of the same name. Guarana is an ingredient of some 'energy' drinks and 'healthy' nutritional products. Both cola nut and guarana contain caffeine as the active constituent. Cocaine is more useful medicinally as a local anaesthetic, but its use as a recreational drug is an increasing problem throughout the world.

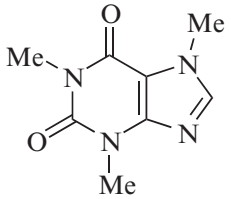
CAFFEINE EU

Caffeine is a methylxanthine derivative found in tea, coffee and cocoa (Fig. 17.4). It is a mild stimulant, and is added to many analgesic preparations to enhance activity, although there is no scientific basis for this practice. High doses may lead to insomnia and a feeling of anxiety, and can induce withdrawal syndrome in severe cases.

COLA NUT, *COLA* SPP. (COLAE SEMEN) EU

Cola, or kola nut [*Cola nitida* (Vent.) Schott et Endl., *Cola acuminata* (Beauv.) Schott et Endl., Sterculiaceae], is native to West Africa and extensively cultivated in the tropics, particularly Nigeria, Brazil and Indonesia. The seed is found in commerce as the dried, fleshy cotyledons, without the testa. They are red-brown in colour, convex on one side and flattened on the other, up to 5 cm long and about 2.5 cm in diameter. The cotyledons of C. *acuminata* are generally smaller and divided into 4 or 6 segments.

Cola contains the xanthine derivative caffeine (Fig. 17.4), with traces of theobromine and theophylline. Tannins and phenolics, including catechin, epicatechin, kolatin, kolatein, kolanin, and amines, including dimethylamine, methylamine, ethylamine and isopentylamine, are also present, together with thiamine and other B vitamins.



Caffeine

Fig. 17.4

Caffeine is a mild stimulant and has diuretic properties; cola extracts are also astringent and antidiarrhoeal due to the tannin content. Cola extracts are an ingredient of many tonics for depression and tiredness, and to stimulate the appetite. Cola extract is safe, apart from any effects due to high doses of caffeine (see above).

GUARANA, *PAULLINIA CUPANA* KUNTH. EX H. B. K

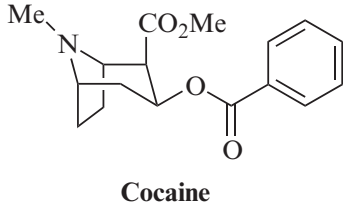
Guarana (Sapindaceae) is a vine indigenous to the Amazonian rain forest. The seeds are ground to a paste and used in cereal bars, or extracted and made into a stimulant drink. The effects are similar to those of cola (see above).The main active constituent is caffeine, which was formerly known as guaranine, and other methyl xanthines. It also contains tannins.

COCAINE EU

Cocaine (Fig. 17.5) is a tropane alkaloid extracted from the leaf of coca [*Erythroxylum coca* Lam. and *E. novogranatense* (Morris) Hieron, Erythroxylaceae]. These are shrubs growing at high altitudes in the South-American Andes. The leaf is still chewed by the local people (along with lime to assist buccal absorption), in order to alleviate symptoms of altitude sickness and fatigue. Cocaine is rarely used medicinally, except as a local anaesthetic in eye surgery, but is now a major illicit drug responsible for many health problems and associated crime. The supply and use of cocaine is strictly regulated in most countries.

ANALGESICS

Two types of analgesics are usually recognized: those that act via the CNS (the opioids) and will be discussed briefly here; the non-opiate and non-steroidal antiinflammatory drugs, which include aspirin, and which will be covered in Chapter 20. It is very common for the two types to be used in combination, for example aspirin with codeine. The opioid analgesics and their derivatives have never been surpassed as painkillers in efficacy or patient acceptability despite their disadvantages. They are obtained from the opium poppy (*Papaver somniferum*) and the most important are still the alkaloids morphine and codeine. Numerous derivatives such as oxycodone, dihydrocodeine, fentanyl, buprenorphine and etorphine have been developed which have different therapeutic and pharmacokinetic profiles, or can be administered via a different route (buccal tablets such as those containing buprenorphine, or transdermal patches, such as with fentanyl). The pharmacology of the opiates is covered in depth in many textbooks and these should be referred to for further information.



Cocaine

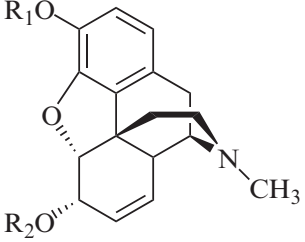
Fig. 17.5

OPIUM, *PAPAVER SOMNIFERUM* L. (OPII CRUDUM; OPII PULVATUS NORMATUS) EU

The opium poppy (*Papaver somniferum*, Papaveraceae) is an annual that is native to Asia, but is cultivated widely for food (the seed and seed oil), for medicinal purposes and as a garden ornamental. It has been used since time immemorial as a painkiller, sedative, cough suppressant and antidiarrhoeal, and features in ancient medical texts, myths and histories. The flowers vary in colour from white to reddish purple, but are usually pale lilac with a purple base spot. The capsules are subspherical, depressed at the top with the radiating stigma in the centre, below which are the valves through which the seeds are dispersed. The seeds are small, greyish and kidney-shaped. The latex, which exudes from the unripe capsule when scored, dries to form a blackish tarry resin, which is known as opium. For pharmaceutical use it can be treated to form 'prepared opium', but opium or the whole dried capsule (known as 'poppy straw') are now used commercially to extract the alkaloids. The supply and use of these products is strictly regulated in most countries. Poppy seeds are used in cooking.

Constituents

Alkaloids represent about 10% of the dried latex. The major alkaloid is morphine (Fig. 17.6), with codeine and thebaine and lesser amounts of very



Morphine, $R_1 = R_2 = H$
Codeine, $R_1 = CH_3$, $R_2 = H$

Fig. 17.6

many others including narceine, narcotine, papaverine, salutaridine, oripavine and sanguinarine.

Therapeutic uses and available evidence

Opium has potent narcotic and analgesic properties. The total alkaloidal extract is known as 'papaveretum' and is used for pre-operative analgesia (now with the narcotine removed due to its reported genotoxicity). Morphine is a very potent analgesic, used for severe pain in the short term (e.g. kidney stone), or for terminal illness, and is the starting material for the production of diamorphine (heroin). Codeine is less potent than morphine, although it is a very useful analgesic for moderate to severe pain, in for example for migraine, dental and gynaecological pain. All the opioid analgesics have side effects, which include nausea, constipation and drowsiness; they cause respiratory depression and have a potential for dependence, which varies according to their capacity to induce euphoria. A withdrawal syndrome is common after illicit use (especially with heroin), but less of a problem with medical use.

MIGRAINE

The aetiology of migraine is not fully known and various drugs are used in its treatment. The analgesics mentioned above (particularly codeine) can be used to relieve an attack, although their capacity to induce nausea can cause problems, and aspirin can cause stomach discomfort. The newer synthetic drugs sumatriptan, naratriptan and others are highly effective in acute attacks, and β-blockers and pizotifen taken regularly are used to prevent recurrences. If all else fails, ergotamine can be used in limit doses for acute attacks. There is, however, one herb that has been investigated as a preventative, and this is feverfew.

ERGOTAMINE

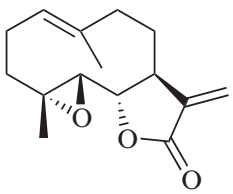
Ergotamine is an alkaloid extracted from ergot (*Claviceps purpurea*), a parasitic fungus that grows on cereals, usually rye. It can be used to treat severe migraine that cannot be controlled with other drugs, but it can cause severe adverse reactions and there are restrictions as to the maximum daily and weekly doses. It is not suitable for children.

FEVERFEW, *TANACETUM PARTHENIUM* (L) SCHULTZ BIP. (TANACETI PARTHENII HERBA) EU

Feverfew [syn. *Chrysanthemum parthenium* (L.) Bernh., Asteraceae] is a perennial herb reaching 60 cm, with a downy erect stem. It has been a common garden plant for many centuries and was found in peasants' gardens throughout Europe. It is still a popular medicinal plant in many parts of the world, to treat rheumatism and menstrual problems. The aerial parts are used. The leaves are yellowish-green, alternate, stalked, ovate and pinnately divided with an entire or crenate margin. The flowers, which appear in June to August, are up to about 2 cm in diameter and arranged in corymbs of up to 30 heads, with white ray florets and yellow disc florets and downy involucral bracts.

Constituents

The sesquiterpene lactones are essential for the biological activity, the major one being parthenolide (Fig. 17.7), with numerous others reported from the species (e.g. santamarine). It also contains small amounts of essential oil (0.02–0.07%), with α-pinene and derivatives, camphor and others.



Parthenolide

Fig. 17.7

Therapeutic uses and available evidence

The main use of feverfew today is as a prophylactic and treatment for migraine. The fresh leaves may be eaten, usually with other foods to disguise the nauseous taste, or a standardized extract taken daily to prevent migraine attacks. Although some clinical studies have shown efficacy, others have not, and further work is needed to identify which extracts may be effective (Pittler and Ernst 2004).

Feverfew extracts inhibit secretion of serotonin from platelet granules and proteins from polymorphonuclear leukocytes (PMNs). Since serotonin is implicated in the aetiology of migraine and PMN secretion is increased in rheumatoid arthritis, these findings substantiate the use of feverfew in these conditions. Parthenolide is considered to be the main active constituent. It is a potent inhibitor of NF-kB. The sesquiterpene lactones as a class have an effect on a large number of other targets, including the inhibition of prostaglandin production and arachidonic acid release. This explains the antiplatelet and antifebrile actions to some extent, but in fact feverfew extract with the parthenolide removed also has antiinflammatory activity (Sur et al 2009). Feverfew may produce side effects such as dermatitis, and soreness or ulceration of the mouth. Also, contact dermatitis has been described, especially by workers handling material from this species, caused by the exposure to the allergenic sesquiterpene lactones.

DRUGS USED FOR COGNITIVE ENHANCEMENT AND IN DEMENTIA

There are few effective treatments for improving memory, especially in dementia. Acetylcholinesterase-inhibiting drugs are available to treat Alzheimer's disease with varying degrees of success. Rivastigmine is a reversible, non-competitive inhibitor of acetylcholinesterase. It is a semi-synthetic derivative of physostigmine, an alkaloid found in the Calabar bean (*Physostigma venenosum*), a highly poisonous plant indigenous to West Africa. Galantamine (= galanthamine), an alkaloid extracted from the snowdrop (*Galanthus nivalis*) was introduced around 2001 (Fig. 17.8, Heinrich and Teoh 2004). These drugs appear to slow down progression of the disease for a period of time, but do not cure it, and have side effects making them unacceptable to many patients.

GINKGO, *GINKGO BILOBA* L. (GINKGO FOLIUM) EU

Ginkgo, the maidenhair tree (Ginkgoaceae), is an ancient 'fossil' tree indigenous to China and Japan and cultivated elsewhere. It is very hardy and is reputed to be the only species to have survived a nuclear explosion. The leaves are glabrous and bilobed, each lobe being triangular with fan-like, prominent, radiate veins. The leaves are used medicinally and the fruits are eaten.

Constituents

Ginkgo contains two major classes of actives, both of which contribute to the activity: ginkgolides A, B and C, and bilobalide, which are diterpene lactones; and the biflavone glycosides such as ginkgetin, isoginkgetin and bilobetin (Fig. 17.9). Ginkgolic acids are present in the fruit but normally only in very minor amounts in the leaf.

Therapeutic uses and available evidence

The most important use of ginkgo is to reduce or prevent memory deterioration, due to ageing and milder forms of dementia, including the early stages of Alzheimer's disease (e.g. Ihl et al 2010). It's enhancement of cognitive processes is thought to be by improving blood circulation to the brain and also due to its antiinflammatory and

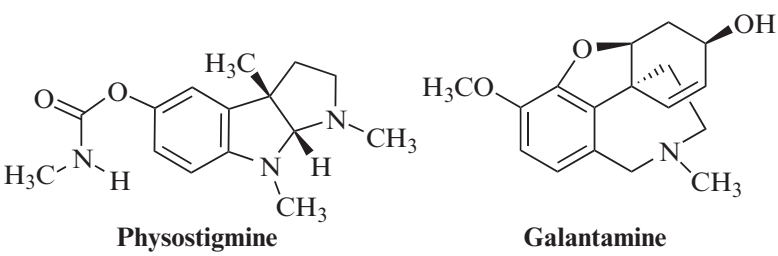


Fig. 17.8

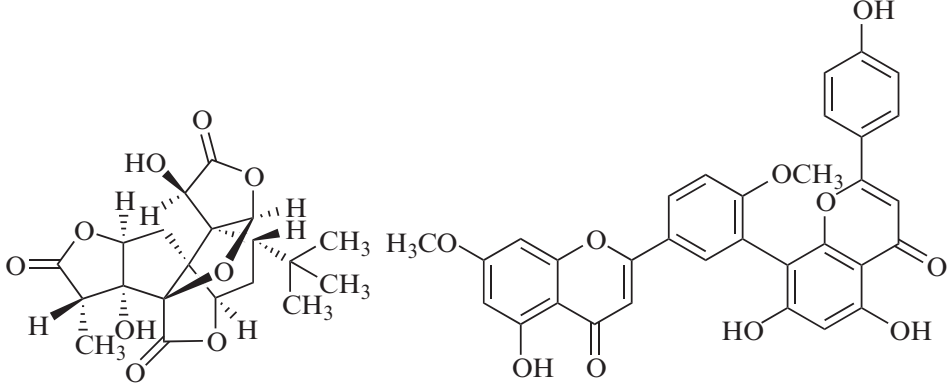


Fig. 17.9

antioxidant effects. Many clinical studies have been carried out (not all of high quality), and the extract has been shown to improve the mental performance in healthy volunteers and geriatric patients where this was impaired (for review, see Weinmann et al 2010). The effects on the CNS are not yet well defined, but include effects on neurotransmitter uptake, neurotransmitter receptor changes during ageing, cerebral ischaemia and neuronal injury. Inhibition of nitric oxide may play a part. The usual dose of ginkgo (standardized) extracts is 120–240 mg daily. Ginkgo has been reported to cause dermatitis and gastrointestinal disturbances in large doses, although rarely. Allergic reactions in sensitive individuals are more likely to be due to ingestion of the fruits due to the ginkgolic acids, which are usually absent from leaf extracts and ginkgo products, or present only in very small amounts.

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Infectious diseases

Plants have been a central part of traditional medicines to cure topical and systemic infections caused by microbes, in particular bacteria. These preparations form the basis of many wound-healing materials in the developing world where the plant is prepared as a crude drug or an extract that is applied topically to improve the healing of a wound. These preparations may have antimicrobial properties and remove the microbes by an antiseptic mechanism and/or they may promote the ability of the wound to repair itself by stimulating cellular growth. Numerous natural products produced by plants also have antiprotozoal and insecticidal activity. Many, especially those containing essential oils, are active against all of these. Intestinal worms can be treated with herbal materials such as wormseed and wormwood (*Artemisia* spp.), but the most effective and least toxic anthelmintic drugs at present are synthetic, so will not be covered here.

There are many reasons why plants are a valuable source of antimicrobial natural products and the most fundamental reason is that they contain intrinsically antimicrobial compounds such as **carvacrol** (Fig. 18.1 and see Chapters 6 and 7) from Thyme (*Thymus vulgaris*, Lamiaceae) which is a monoterpene and is present in the essential oil of this species.

This phenolic monoterpene has a range of antibacterial and antifungal properties (Baser 2008) and may be produced by the plant to protect itself from attack from plant pathogenic microbes and insects that are present in its environment. This is an example of an **intrinsic** or **latent antimicrobial** natural product that the plant produces as a normal part of its chemistry which can be used medicinally. Plants also have the ability to produce antimicrobial natural products when they are under attack from microbes, herbivores and insects. These compounds are very quickly synthesized by the plant and are called **phytoalexins** which display antimicrobial properties to a wide range of bacteria and fungi. Examples of this phenomenon include the potato, which when inoculated with a fungus synthesizes the antimicrobial coumarin **scopoletin** (Fig. 18.2 and Chapter 6) and the bisbenzyl compound (**3,5-dihydroxy-bisbenzyl**) also depicted in Fig. 18.2, which is produced by a species of yam (*Dioscorea rotundata*, Dioscoreaceae).

This bisbenzyl is very strongly active against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa* and *Escherichia coli* with minimum inhibitory concentrations of 10 mg/L (Fagboun et al 1987). This is astounding activity, particularly against Gram-negative bacteria such as *E. coli* and *P. aeruginosa* which are often impervious to plant antimicrobials.

Plants are also used extensively as topical antimicrobials in many societies and there is an enormous body of primary literature in journals that specialize in ethnomedical research such as the *Journal of Ethnopharmacology*. In the North-Eastern part of Australia the indigenous peoples use the aerial parts of *Eremophila duttonii* (Myoporaceae) as a topical antibacterial preparation (Smith et al 2007) and the active constituent has been isolated and characterized as an unusual serrulatane diterpene (Fig. 18.3).

This compound had activity against *S. aureus* and *S. epidermidis*, both of which are commensal bacteria, common skin organisms and major causative agents in wound infections. It was also active towards the

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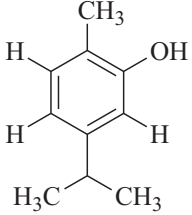
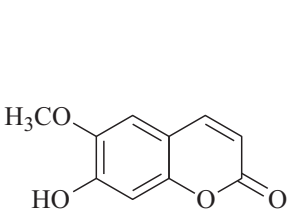
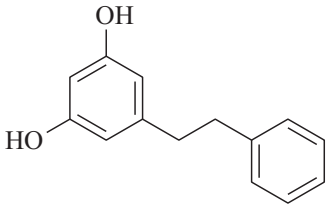


Carvacrol

Fig. 18.1

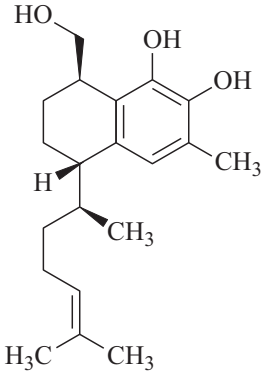


Scopoletin



3,5-dihydroxy-bisbenzyl from *Dioscorea rotundata*

Fig. 18.2



Serrulatane diterpene from *Eremophila duttonii*

Fig. 18.3

respiratory pathogen *Streptococcus pneumonia*, one of the main causative agents of pneumonia in adults and children.

Probably the most important reasons that plants produce antibacterial natural products, and why they could be a valuable resource of antimicrobial materials, is that these chemicals are often exceptionally diverse, have stereochemical centres and have extensive functional group chemistry. These factors mean that the compounds will have very distinct shapes, developed by nature over millions of years to bind to protein and DNA targets, and *consequently having an inherent biological activity*. The readers are urged to consult a new and very important review on natural products highlighting this topic written by Professor Giovanni Appendino and colleagues (Appendino et al 2010). Plant antibacterials are very different in shape and chemistry to existing antibacterial chemotypes (Gibbons 2004, 2008), that are often microbially derived such as erythromycin (Fig. 6.11, Chapter 6) and tetracycline (Fig. 6.8, Chapter 6). This may mean that plant-derived antibacterials could function through a different and as yet undetermined mechanism of action. This would make them valuable where bacterial resistance to conventional antibiotics (beta-lactams, macrolides, tetracyclines) has arisen as these bacteria may be susceptible to these agents by working in a very different way. New agents that function by a different mechanism are currently needed, particularly in bacterial infections such as tuberculosis where the causative organism, *Mycobacterium tuberculosis* may possess multiple resistance to existing antibiotics of choice.

The last reason to look at plants as new antimicrobials is because there are already a number of products and preparations that are on the market. These range in type from food-based materials such as the practically ubiquitous Cranberry products marketed as fruit juices, which may also be used in the management of urinary tract infections, through to high-quality phytomedicines containing bearberry that are used for similar ailments.

We will look at some of the common herbs that are used as antimicrobial products and then cover some of the pure single chemical entities (SCEs) that display promising antimicrobial action.

BROAD-SPECTRUM ANTIMICROBIAL AGENTS

UMCKALOABO (PELARGONIUM), *PELARGONIUM SIDOIDES* DC AND *P. RENIFORME* CURT (PELARGONII RADIX)

Umckaloabo means 'useful for deep cough' in Zulu and this term refers to a medicine used traditionally in South Africa as a treatment for respiratory tract infections. This material is derived from the roots of either *Pelargonium sidoides* or *Pelargonium reniforme* from the Geraniaceae plant family. A decoction of the roots is used to treat chest infections and this material is the subject of a book by Charles Stevens ('Stevens Cure'), a 19th century army officer who contracted pulmonary tuberculosis in

London at the end of the 19th century. He was advised by his physician to move to South Africa where the air quality was much better than in Victorian London which was plagued by 'smog'. Whilst in South Africa he received the Umckaloabo preparation from a traditional healer and this cleared his TB infection. Stevens returned to the United Kingdom and marketed a preparation for TB known as Stevens Consumption Cure.

Constituents

The main active components are hydrolysable tannins, (+)-catechin, gallic acid and methyl gallate, including a unique series of O-galloyl-C-glucosyl-flavones. Flavonoids including myricetin and quercetin-3-O-beta-d-glucoside, coumarins including scopoletin, umckalin, 5,6,7-trimethoxycoumarin and 6,8-dihydroxy-5,7-dimethoxycoumarin, are present in both species. A series of benzopyranones has been isolated from *P. sidiodes*, and the pelargoniins (a type of ellagitannin) and a diterpene, reniformin, have been found in *P. reniforme*.

Therapeutic uses and available evidence

Extracts of *Pelargonium* species have been shown to inhibit the adherence of bacteria to cells of the mucous membrane and there is some published chemistry and biology on methoxylated coumarins (Fig. 18.4) from *P. sidoides* which have weak antibacterial activity (Kayser and Kolodziej 1997). They have also been shown to interfere with viral replication (Michaelis et al 2011) and to inhibit viral adherence to cells of mucous membrane and to loosen viscous mucus in the respiratory tract. It has also been postulated that these extracts have immunomodulatory properties. There have been some small clinical trials on efficacy in reducing the symptoms associated with tonsillitis and bronchitis, particularly amongst children (Matthys et al 2007). These materials are not, however, a replacement for antibiotics, but they may be used as a supplement to ameliorate the symptoms associated with inflammation of the upper respiratory tract (URT).

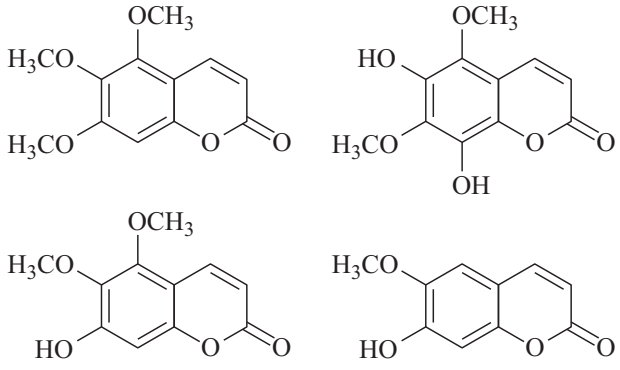


Fig. 18.4

An ethanolic extract of *Pelargonium sidoides* is currently marketed by the phytopharmaceutical company Schwabe under the trade name Kaloba. This preparation is marketed to relieve the symptoms of common cold, sore throats and coughs based on long-standing use as a traditional remedy. A number of general practitioners recommend Kaloba as a preparation to reduce the symptoms of soreness associated with URT infections. This extract is also given to athletes to help strengthen the immune system, which can be compromised by extreme exercise, to protect against colds. A study in athletes submitted to intense physical activity found that *Pelargonium sidioides* increased the production of secretory immunoglobulin A in saliva, and decreased levels of both interleukin-15 and interleukin-6 in serum, suggesting a strong modulating influence on the immune response associated with the upper airway mucosa (Luna et al 2011).

There has also been a study on extracts demonstrating weak antibacterial activity which is due to the presence of the ubiquitous unsaturated fatty acids oleic and linoleic acid against fast-growing species of *Mycobacterium*; however these compounds are unlikely to be responsible for the 'anti-TB' activity of Steven's cure (Seidel and Taylor 2004).

LEMON BALM, *MELISSA OFFICINALIS* L. (MELISSAE FOLIUM) EU

This plant is a member of the Lamiaceae plant family and has white flowers and the leaves have a highly pungent and aromatic smell being one of the most popular fragrances due to the essential oil of this species. Unfortunately, the plant produces very little essential oil and this accounts for the high cost of genuine lemon balm oil. This species contains phenolic compounds and the oil is rich in mono- and sesquiterpenes and the plant has long use as an antimicrobial and carminative and mild sedative.

There are a number of topical formulations which are marketed for *Herpes simplex* virus skin lesions and there are clinical data and some *in vitro* activity has been confirmed with the extracts of *Melissa officinalis* (Koytchev et al 1999). The herb is generally

well-tolerated, although it has been suggested that long-term use may interfere with thyroid function.

Constituents

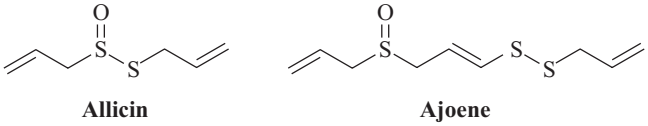
Both the polyphenolics and the essential oil are thought to be responsible for the antimicrobial effects. Phenolics include protocatechuic acid, caffeic acid, rosmarinic acid and tannins, in significant amounts, together with flavonoids such as cynaroside, cosmosiin, isoquercitrin and others. The volatile oil consists mainly of α- and β-citral (= neral and geranial), with caryophyllene oxide, linalool, citronellal, nerol, geraniol, germacrene-D, traces of eugenyl acetate, *cis*- and *trans*-β-ocimene, copaene and others.

Therapeutic uses and available evidence

Lemon balm is antimicrobial, carminative and sedative. Hot water extracts have antiviral properties, mainly due to the polyphenolic acids. Topical formulations are used for *Herpes simplex* virus skin lesions, the antiviral activity having been confirmed *in vitro* and also by clinical trial. Aqueous extracts also inhibit division of tumour cells, and tannin-free extracts inhibit protein biosynthesis (for review, see Ulbricht et al 2005). The herb is used as an ingredient of herbal teas, often with other herbs, for nervous disorders and insomnia (see Chapter 17). Lemon balm is well tolerated, although it should not be taken internally in high doses over a long period because of its reputed antithyroid activity.

GARLIC, *ALLIUM SATIVUM* L. (ALLII SATIVI BULBUS) EU

Garlic, and other *Allium* spp. (Alliaceae), have a very long history as both a topical and systemic material to treat various infections. The literature is full of in vitro studies showing efficacy of the extracts and oils of the bulbs of various *Allium* species with activity against various bacteria, fungi and viruses. The family has a long and rich usage as culinary herbs with onions, garlic, shallots and chives all producing antimicrobial sulphur containing natural products, typified by **allicin** and **ajoene** (Fig. 18.5).



Allicin **Ajoene**

Fig. 18.5

Garlic has been used clinically for the treatment of tuberculosis with some success in the United States in the 1940s and it has been referred to as Russian penicillin, as a result of its wide use in the former Soviet Union, again with some considerable success as an antibacterial (Bolton et al 1982). The widespread use of garlic has prompted recent investigation of other species which may harbour useful natural products and a number of interesting sulphur-containing antibacterials with very potent antibacterial activity have been isolated, such as the unusual pyridine-*N*-oxide natural products from *Allium stipitatum* (Fig. 18.6, O'Donnell et al 2009). These compounds displayed activity against slow- and fast-growing mycobacteria and a range of *Staphylococcus aureus* species some of which were methicillin-resistant and multidrug-resistant.

Compound 18.6 was also active against *Mycobacterium tuberculosis* with a minimum inhibitory concentration of 0.1 mg/L showing the potential of these natural products and garlic metabolites in general as anti-TB drug-leads.

Constituents

The antimicrobial constituents are the sulphur compounds, which include allicin, allylmethyl trisulphide, diallyl disulphide, diallyl trisulphide, diallyl tetrasulphide, allylpropyl disulphide, and glycosides such as sativoside B1. There are also monoterpenoids present (citral, geraniol, linalool and α- and β-phellandrene) and flavonoids based on kaempferol and quercetin. It is possible that the bulbs of these species, which are the subterranean part of the plant that is the key to reproduction, produce these sulphur natural products as a protection against microbes in their environment.

Therapeutic uses and available evidence

Garlic extracts have been shown to have antibiotic, expectorant and anti-thrombotic properties and many garlic preparations are marketed for their anti-blood clotting properties and to give some protection against atherosclerosis. Preparations from common garlic have also found much use in the treatment for respiratory tract infections, such as common cold, flu and bronchitis. The allyl sulphides, such as allicin and ajoene, are strongly antimicrobial having activity against *Staphylococcus aureus*, *Streptococcus* species and even some Gram-negative bacteria, such as *Helicobacter pylori*, the major bacterial causative agent of stomach ulcers (Harris et al 2001).

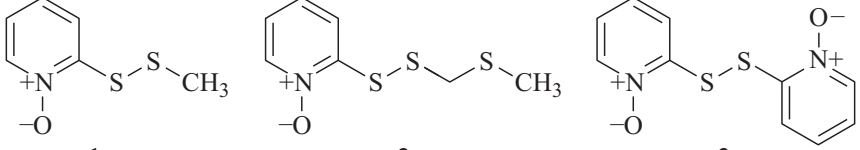


Fig. 18.6

Garlic preparations are generally very well tolerated with low toxicity (other than offensive smell!), although it has been suggested that these materials may have the ability to interfere with anti-platelet drugs.

TEA TREE AND TEA TREE OIL, *MELALEUCA ALTERNIFOLIA* (MAIDEN ET BETCHE.) CHEEL (*MELALEUCAE ATHEROLEUM*)

The oil from the leaves and stems of this tree has a long history of traditional usage amongst indigenous peoples of North Australia and New South Wales. This tree grows with other species of Myrtaceae, such as *Eucalyptus*, which are also used topically as an antimicrobial medicine. Over the last 20 years there has been an explosion of usage of tea tree oil products in Europe and the United States and one cannot go into a pharmacy without seeing dozens of preparations including soaps, shampoos, creams, lotions and gels containing this oil, which has a distinctive 'dry' aroma. The leaves and twigs undergo distillation to produce the oil which is pale yellow to colourless. Traditionally the oil is used topically as an antimicrobial for skin infections, to reduce bruising and for insect bites.

Constituents

Tea tree oil is a highly complex mixture of monoterpenes and the major component is terpinen-4-ol (Fig. 18.7), that may be present at concentrations as high as 30%.

Some varieties are rich in 1,8-cineole which is present in *Eucalyptus* oil but the best quality tea tree oils are low in 1,8-cineole and are high in terpinen-4-ol. Other monoterpenes present include γ- and α-terpineol, α- and β-pinene, α-terpineol, limonene and cymene, and the sesquiterpenes cubebol, epicubebol, cubenol, epicubanol and δ-cadinene. The composition of the oil may also depend on the method of distillation.

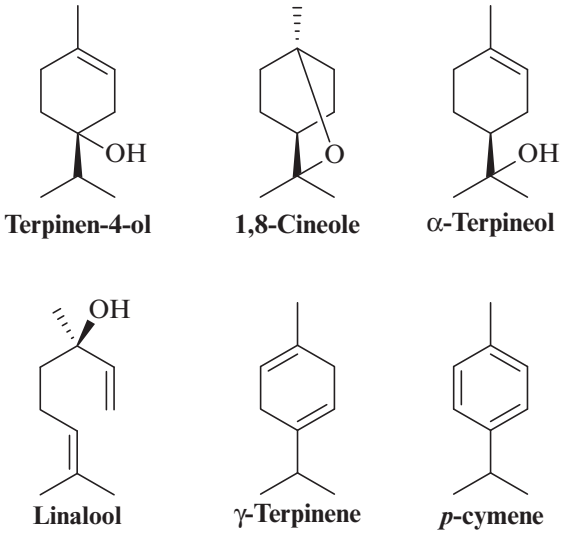


Fig. 18.7

Therapeutic uses and available evidence

Tea tree oil is now used worldwide in the form of skin creams for pimples and acne, pessaries for vaginal thrush, as an inhalation for respiratory disorders and in pastilles for sore throats. It is also popular as a lotion for the treatment of lice and scabies infestations, and for dandruff and other hair and scalp disorders. The oil has broad-spectrum antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and various pathogenic fungi and yeasts including *Candida albicans*, and also against the protozoa *Leishmania major* and *Trypanosoma brucei*. There have also been studies conducted at using preparations containing the oil to reduce the spread of MRSA in hospital units (Warnke et al 2009) and there has been much research into the use of this oil as an antiseptic for nursing staff. The most active purified compounds from this oil include terpinen-4-ol, γ-terpinene, α-terpineol and linalool with minimum inhibitory concentrations in the range of 0.125–0.25% v/v (Carson and Riley 1995, Cox et al 2001, Raman et al 1995). These compounds also demonstrated broad-spectrum activity towards Gram-negative bacteria. It was also shown that the non-oxygenated monoterpenes such as γ-terpinene

and *p*-cymene (Fig. X.7) reduced the efficacy of terpinen-4-ol by reducing its aqueous solubility (Cox et al 2001). Clinical trials have supported many of the uses of tea tree oil, including for *Herpes labialis*, although most of the studies are rather small (see Carson et al 2006). Undiluted essential oils can cause skin irritation and tea tree oil should be used with care. It should only be taken internally in small doses.

The related manuka tree (*Leptospermum scoparium* J. R. Forst. et G. Forst.) is sometimes referred to as 'New Zealand tea tree', and used for similar purposes.

BEARBERRY, *ARCTOSTAPHYLOS UVA-URSI* L. (UVAE URSI FOLIUM) EU

The leaves of the shrub *Arctostaphylos uva-ursi* (Ericaceae), widely known as Uva Ursi or bearberry, are used to treat cystitis and urethritis, although their use is not supported by evidence from randomized controlled trials.

Constituents

The main constituents are hydroquinone derivatives, notably the glycoside **arbutin**. This compound is hydrolysed in vivo by the enzyme β-glucosidase to give the diphenol, **hydroquinone** (Fig. 18.8). Other constituents include terpenoids such as α- and β-amyrin, flavonoids and tannins.

Therapeutic uses and available evidence

Hydroquinone is the main active component of this material and is a potent phenolic antiseptic. This compound is very active against many bacteria, but in particular those that are liable to cause urinary tract infections such as *Escherichia coli* and *Pseudomonas aeruginosa*. Activity has also been demonstrated against other species such as *Bacillus subtilis* and *Staphylococcus aureus*. Arbutin is hydrolysed by β-glucosidase to yield the active principle hydroquinone, which has antiseptic and astringent properties. Uva-ursi is also mildly diuretic and antilithuric (Beaux et al 1999). Uva ursi preparations such as Arctuvan require that the urine is alkaline for it to have antiseptic properties and, as such, acidic foods including cranberry juice (see below) should be avoided during treatment. Hydroquinone is a very reactive and biologically active compound and is cytotoxic and mutagenic. High doses and prolonged usage of bearberry products should be avoided and it should not be used during pregnancy or by anyone who has a kidney infection.

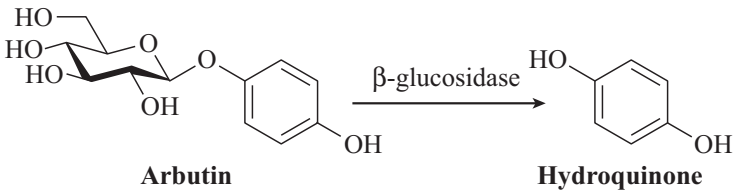
CRANBERRY JUICE, *VACCINIUM MACROCARPON* AITON

This is one of the most popular of the plant-derived products with preparations generally being taken in the form of the juice of the berries of *V. macrocarpon* and related species (Ericaceae) or a freeze-dried extract which is then re-suspended in water. Medicinally the berries have been used to treat urinary tract infections and the species is an American plant used traditionally for this purpose. Marketed products include the highly popular Ocean Spray Cranberry Classic and many different fruit juice variants of this product.

Constituents

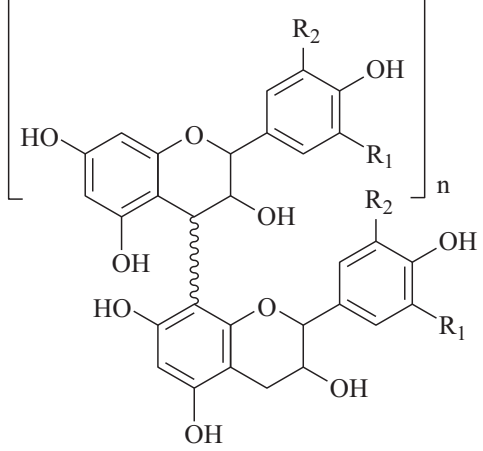
The chemistry of this plant is still not well understood because it contains many **flavonoid polymers**, in particular the **proanthocyanidins** that are believed to be important for the antibacterial activity of this species (Fig. 18.9).

These proanthocyanidins are exceptionally complex and vary in the number of flavonoid units in the polymer (n may vary considerably in Fig. 18.9), the way in which each of the units is connected and the functional groups present on each unit (R_1 and R_2 groups in the figure may be OH or OMe for example). This can give rise to a highly complex natural product mixture. These compounds are also polar and soluble in water, ethanol and methanol, which can make their analysis by conventional methods such as HPLC and HPLC-MS difficult.



Arbutin **Hydroquinone**

Fig. 18.8



Proanthocyanidins

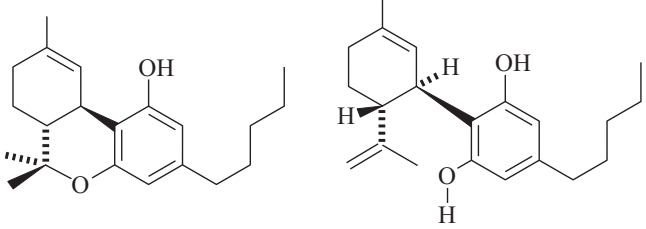
Fig. 18.9

Therapeutic uses and available evidence

In-vitro experiments with cranberry juice and proanthocyanidins have shown that they have the ability to affect the binding of the bacterium *Escherichia coli*, which is a major causative agent of urinary tract infections, to uroepithelial cells, therefore, inhibition adherence of this bacterium allowing its clearance. Cranberry juice is also thought to act by increasing levels of hippuric acid (a metabolite of benzoic acid) and, therefore, acidity of the urine. Clinical studies of cranberry juice have provided equivocal evidence for prevention or treatment of UTIs and the efficacy remains unproven (see Jepson and Craig 2008). Cranberry juice has a high calorific content, and patients with diabetes who wish to use cranberry juice should use sugar-free preparations. Reports that cranberry juice interacts with warfarin are controversial, and are now considered to be unproven (Zikria et al 2010). Cranberries have also been used for unrelated disorders such as kidney stones, and are frequently used in foods.

SINGLE CHEMICAL ENTITY (SCE) AND NOVEL PLANT ANTIBACTERIALS

So far we have looked at herbal products and their extracts as antibacterials, but there is a growing body of literature describing the activities associated with single compounds isolated in bioassay-guided fractionation studies on plants (Gibbons 2004, 2008). These plants may result from random screening,



Tetrahydrocannabinol **Cannabidiol**

Fig. 18.10

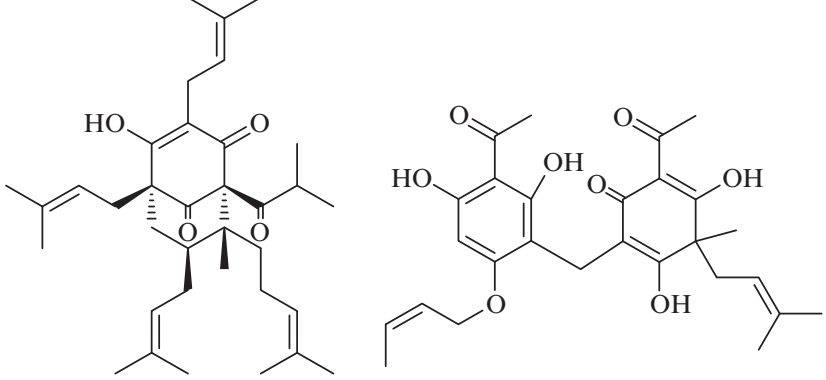
from a traditional antibacterial use of the plant or the plant material may have been treated prior to the study to elicit phytoalexins.

Cannabis sativa has a long history of use as a medicinal material having not only euphoriant, but also antiseptic properties. In Afghanistan there is anecdotal usage of cannabis resin to treat plague and as a topical antimicrobial preparation. There is in vitro evidence to support the antibacterial properties of cannabis as the major components, **tetrahydrocannabinol** and **cannabidiol** (Fig. 18.10) are highly active against Gram-positive bacteria such as *Staphylococcus aureus* and its methicillin-resistant (MRSA) variants (Appendino et al. 2008).

Cannabidiol has the added advantage of also displaying anti-inflammatory activity and this would certainly be advantageous as a wound healing/cleansing preparation. Given the recent marketing authorization in the UK and Canada for Sativex, a licensed cannabis-based medicine used to ameliorate the pain and spasticity associated with multiple sclerosis (MS), there is real opportunity to develop new cannabis-based antibacterials.

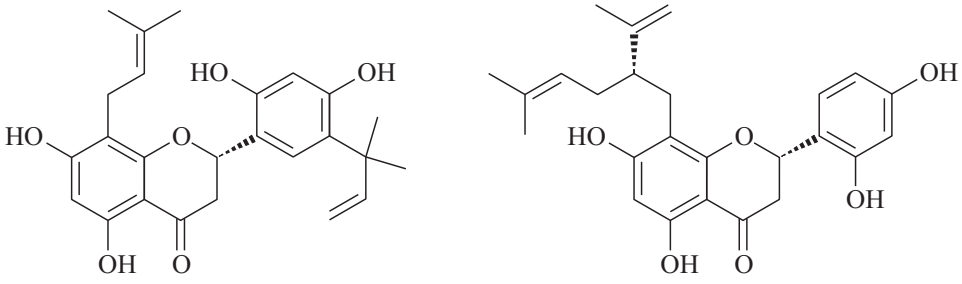
There has also been some work on the acylphloroglucinol group of natural products and one of the first members of this class to be elucidated was hyperforin (Fig. 18.11), from St John's wort. This metabolite was studied due to its excellent activity against penicillin- and methicillin-resistant *Staphylococcus aureus* strains with MIC values being 0.1–1 mg/l (Schempp et al 1999).

The acylphloroglucinols are relatively complex natural products based on a cyclic aromatic-derived core with many prenyl groups, which may be either cyclized or oxidized to give a highly functional group rich and chiral class of products such as hyperforin. Other examples from this group include the drummondins (Fig. 18.11) from another species of *Hypericum*, *H. drummondii*, which had potent activity (MIC = 0.39 mg/l, Jayasuriya et al 1991).



Hyperforin Drummondin E

Fig. 18.11



1 2 Sophoraflavone G

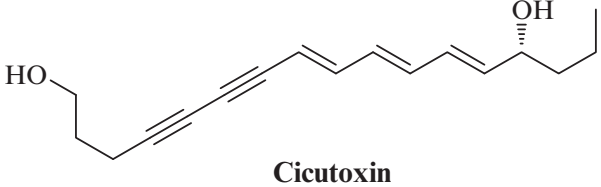
Fig. 18.12

The flavonoids are probably the most intensively studied natural products in terms of their antimicrobial activity and the flavanones, for example compound **1** (Fig. 18.12), within this class have some very interesting levels of potency and action. Many of these natural products possess prenyl or geranyl groups that presumably contribute to the lipophilicity and membrane solubility of these compounds. This could improve their cellular uptake and enhance their ability to penetrate the bacterial cell.

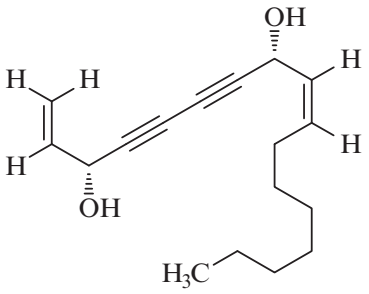
Compound **1** has excellent potency toward MRSA strains with MIC values of 1.5 mg/l and compound **2** is sophoraflavanone G, which is antibacterial in its own right (MIC = 3.1 mg/l) and also has strong synergism in combination with the glycopeptide antibiotic vancomycin, which is used clinically to treat MRSA infections (Sakagami et al 1998). A combination of sophoraflavanone G with vancomycin could feasibly contribute to better treatment of an MRSA infection and it is conceivable that these lipophilic compounds could be formulated into a topical antiseptic preparation to help with decolonization.

Plants within the Apiaceae family, which includes carrot, coriander, parsnip, caraway and dill, are known to produce polyacetylenic natural products. These compounds have conjugated triple bonds (acetylenes). Some of these metabolites are deadly poisonous, such as **cicutoxin** from Cowbane (*Cicuta virosa*), whereas others such as **falcarindiol** (Fig. 18.13) are present in the roots of these plants and are probably synthesized as a protection against microbes in their environment.

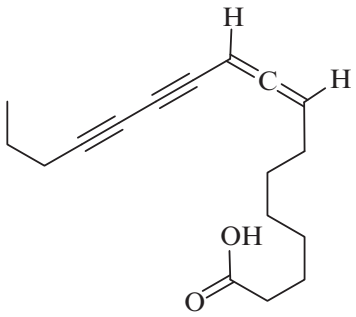
Falcarindiol has a similar shape to **phomallenic acid B**, a fungal-derived antibacterial natural product which has been shown to be an inhibitor of fatty acid synthase-2 (FAS-II) and it is possible that falcarindiol functions in a similar fashion. Falcarindiol is present in many Chinese medicinal plants, and one of these, *Angelica dahurica*, is used to treat acne and this metabolite may in part be responsible for this action as the main bacterial causative agents of acne are the staphylococci and *Propionibacterium acnes*.



Cicutoxin



Falcarindiol
MIC = 12.5 mg/L



Phomallenic acid B
MIC = 12.5 mg/L

Fig. 18.13

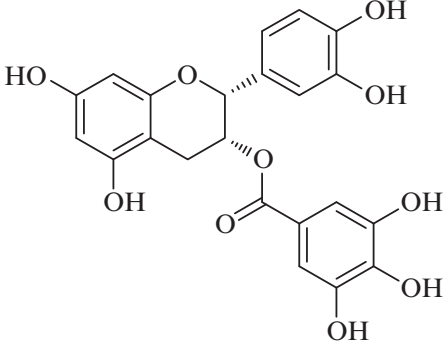
We have already seen that some natural products such as sophoraflavanone G have the ability to potentiate the action of existing antibacterial agents. Bacteria have the ability to remove antibiotics from their cells by a process known as efflux that can make the antibiotic inactive against that strain. Such effluxing strains have proteins on their cell membranes which transport the antibiotics out of the bacterial cell. Some natural products (Fig. 18.14) have been found to inhibit these proteins and stop them from removing the antibiotic and such an action has the potential to restore antibiotic activity.

Plant natural products with the ability to inhibit these processes include tea catechins such as epicatechin gallate, simple diterpenes like totarol, alkaloids such as reserpine and even complex resin oligosaccharides (Fig. 18.14) (Stavri et al 2007).

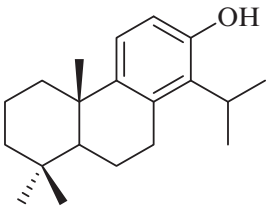
There is great potential to discover new antimicrobial substances from plants and the chemistry presented by plant sources is very often highly functional and chiral, and these facets are desirable in a drug-lead candidate, assuming supply issues can be overcome. Studies on plant antibacterials require greater depth, particularly with respect to mammalian cytotoxicity (selectivity between microbial and mammalian toxicity) and mechanism of action. Once these issues have been addressed, it is highly likely that plant sources will generate new antimicrobial chemotypes.

ANTIPROTOZOAL AGENTS

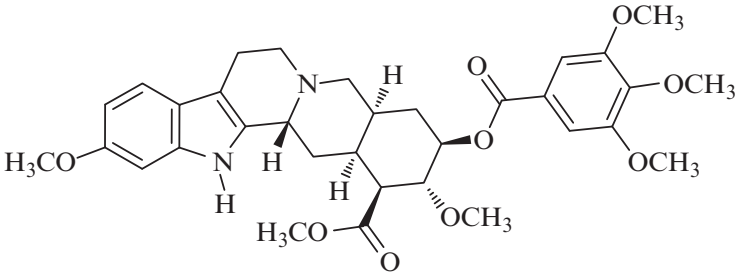
The classical antiprotozoal drug, used to treat malaria, is quinine, from *Cinchona* bark. It is still occasionally used to treat the disease, but more importantly it is the template for the production of newer semi-synthetics such as chloroquine and mefloquine, and others now under development. Most of these are also used for malaria prophylaxis. The most recent antimalarial to be introduced clinically is artemisinin (from sweet or annual wormwood, *Artemisia annua*) or the more stable derivative, artemether. Lapacho (taheebo) contains quinones, which are antiprotozoal, although it is often used in South America as an anticancer treatment. Ebony wood (from *Diospyros* spp.) contains naphthoquinones which are used in a similar way by local peoples. Emetine, an alkaloid from *Cephaelis ipecacuanha*, is amoebicidal, but too toxic for clinical use; however, investigations continue into the effect of similar, semi-synthetic compounds for further development. Most of the important protozoal diseases are endemic in the tropics (e.g. bacillary dysentery), and many (e.g. *Leishmania*) involve a non-human vector, which may be an insect, larva or snail. Control of these diseases, therefore, includes the use of pesticides to destroy the vector, improvement in hygiene and water supplies, as well as targeting the parasite. For many developing countries, the



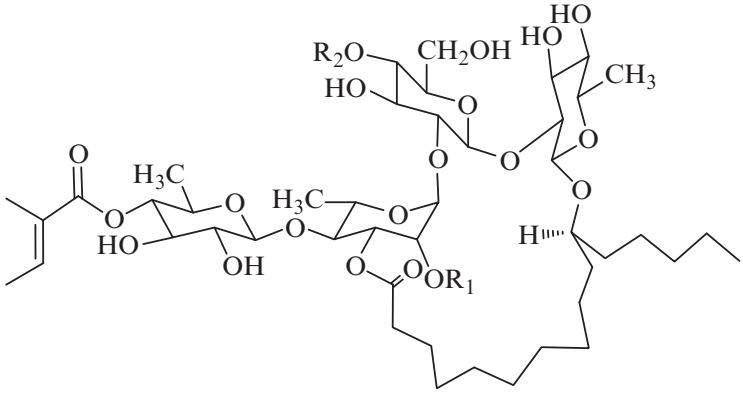
Epicatechin gallate



Totarol



Reserpine



Resin oligosaccharide

Fig. 18.14

use of plant-based antiprotozoals and pesticides represents the best chance of some sort of disease control.

CINCHONA, *CINCHONA* SPP. (CINCHONAE CORTEX) EU

Trees of the genus *Cinchona* (Rubiaceae) are used as a source of quinine (for structure, see Chapter 1). Red cinchona, 'cinchona rubra', is *C. pubescens* (= *C. succirubra* Pavon); yellow cinchona, 'cinchona flava', is *C. calisaya Wedd*., or *C. ledgeriana* Moens. et Trim. Other species and hybrids of the genus *Cinchona* are also used. It has been called Peruvian bark, from the country of origin, and also Jesuit's bark, since it was originally introduced into Europe by Jesuit missionaries. It is native to mountainous regions of tropical America, and cultivated in South-East Asia and parts of Africa. The bark is found in commerce as quills or flat pieces.

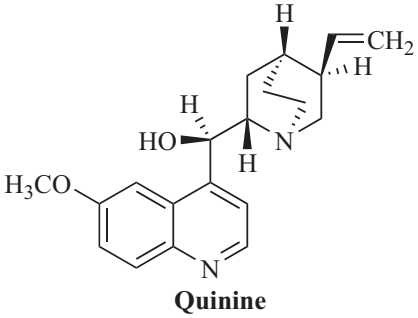
The external surface is brownish-grey, usually fissured, and lichens and mosses may be seen as greyish-white or greenish patches.

Constituents

The actives are quinoline alkaloids, the major being quinine (Fig. 18.15), with quinidine, cinchonine, cinchonidine, epi and hydro derivatives of these, quinamine and others. The total alkaloid content of the bark should be not less than 6.5%, with 30–60% being of the quinine type. Identification is by thin-layer chromatography (TLC). The alkaloids are fluorescent.

Therapeutic uses and available evidence

Quinine was primarily used as an antimalarial before the advent of semi-synthetics, which have improved efficacy, especially against resistant strains, different pharmacokinetic profiles and reduced toxicity. The bark was formerly used as a febrifuge, tonic, orexigenic, spasmolytic and astringent, but it is only used now for the extraction of the alkaloids, quinine and its isomer quinidine. Both quinine and quinidine have antimalarial activity, although quinine is more widely used. Both are cardiac anti-arrhythmic agents (see Chapter 15), which limits their usefulness as antimalarials, and quinidine is still used clinically for this purpose. Quinine salts are used for the prevention of night cramps (the dose for this purpose is 200–300 mg of quinine sulphate or bisulphate) and in low doses is an ingredient of some analgesic and cold and flu remedies. Chronic overdosage can result in the condition known as cinchonism, which is characterized by headache, abdominal pain, rashes and visual disturbances. Cinchona and quinine should not be taken in large doses during pregnancy except for treating malaria.



Quinine

Fig. 18.15

LAPACHO (TAHEEBO, PAU D'ARCO), *TABEBUIA* SPP.

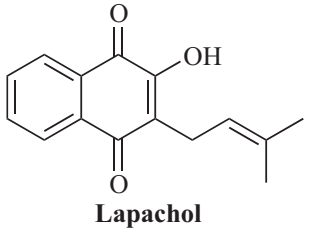
Lapacho is obtained from several species of *Tabebuia* (Bignoniaceae), including T. *avellanedae Lorentz ex Griseb.*, *T. rosea* Bertol., T. *serratifolia* (Vahl) Nicholson and others. These are large tropical trees, indigenous to South America. The inner bark is used medicinally. Lapacho is used traditionally for infectious diseases, including protozoal, bacterial, fungal and viral infections, to enhance immune function and for treating various cancers. Lapachol is antiprotozoal against *Leishmania, Trypanosoma* and *Schistosoma* spp., as well as being antiinflammatory.

Constituents

The active constituents are naphthoquinones, the most important being lapachol (Fig. 18.16), with deoxylapachol, α- and β-lapachone and others. It also contains anthraquinones, benzoic acid and benzaldehyde derivatives.

Therapeutic uses and available evidence

Antimicrobial effects are documented against *Candida, Brucella* and *Staphylococcus* spp., and for several viruses. Lapacho is also becoming popular as an anticancer treatment; antitumour activity has been shown in vitro and in vivo and a few uncontrolled trials have been carried out. The evidence available so far is inconclusive and this botanical drug should not be recommended for the treatment of cancer. Semi-synthetic derivatives of lapachol are being prepared in order to increase activity and reduce toxicity. Lapachol is cytotoxic in large doses, and inhibits pregnancy in mice; however, there is little evidence of toxicity for the herb when used in normal doses. For review, see Gómez Castellanos et al 2009.



Lapachol

Fig. 18.16

SWEET WORMWOOD (SYN. QINGHAOU), *ARTEMISIA ANNUA* L.

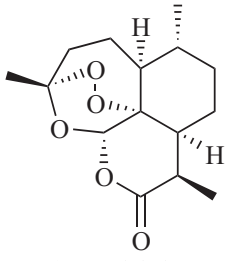
Qinghaou (*Artemisia annua* L.), also known as annual wormwood, is a native of temperate parts of Asia, particularly China. It is a prostrate or erect annual with woody stems, pinnately divided leaves and small yellow flowers arranged in panicles. It has a characteristic sweet, aromatic, odour. The herb has been used for thousands of years in China for fevers and disorders of the liver. It is highly effective for the treatment of malaria, especially against resistant strains of *Plasmodium berghei* and *P. falciparum*, and this is now the major use of the plant.

Constituents

The herb contains sesquiterpene lactones, the most important of which is artemisinin (qinghaosu; Fig. 18.17), as well as the arteannuins A–O, artemisitine, artemisinic acid, hydroarteannuin, and others. There is also a volatile oil containing artemisia ketone, cadinene and others, and flavonoids including artemetin.

Therapeutic uses and available evidence

Artemisinin is one of the most rapidly acting antiplasmodial compounds known. Several more stable and effective derivatives, such as artemether, arteether and artesunate have been developed and are being used clinically for both the prophylaxis and treatment of malaria (see Cui and Su 2009). The herb appears to be fairly non-toxic, although cytotoxicity in vitro and teratogenic effects have been observed in mice. There is evidence that the whole herb extract may be superior to isolated artemisinin, since the flavonoids present in the leaves have been linked to suppression of CYP450 enzymes responsible for altering the absorption and metabolism of artemisinin in the body, and also to a beneficial immunomodulatory activity in subjects afflicted with parasitic and chronic diseases (Ferreira et al 2010).



Artemisinin

Fig. 18.17

INSECTICIDAL AGENTS

PYRETHRUM (INSECT) FLOWERS, *CHRYSANTHEMUM* SPP.

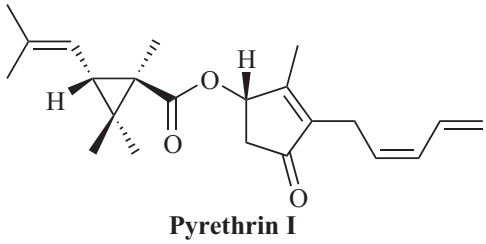
Chrysanthemum cinerariaefolium (Trev.) Vis., *C. coccineum* Willd. and *C. marshallii* Aschers (Asteraceae) are all known as insect flowers. Dalmation insect flowers are *C. cinerariifolium* [formerly *Pyrethrum cinerarii folium* Trev. or *Tanacetum cinerariifolium* (Trev.) Sch. Bip.]; *C. coccineum* and *C. marshallii* are known as Persian and Causasian insect flowers, respectively. They are indigenous to the Balkans but widely cultivated elsewhere. The unopened flower heads are used; they are about 7 cm in diameter, with creamy-white ligulate florets and yellow tubular florets. There are two or three rows of lanceolate greenish-yellow, hairy bracts and a flat receptacle without paleae.

Constituents

All species contain pyrethrins, which are esters of chrysanthemic and pyrethric acids and are the actives. They are known as pyrethrins I (Fig. 18.18) and II, cinerins I and II and jasmolins I and II.

Therapeutic uses and available evidence

The natural pyrethrins are used to treat lice and scabies infestations and to kill other types of insect (houseflies, etc.) which are not necessarily causes of skin infestation. Pyrethrin I is the most potent of the naturally occurring compounds, although all have a knockdown effect on insects. The natural products have been used to develop semi-synthetic derivatives such as permethrin, phenothrin, tetramethrin, cypermethrin and decamethrin, which can be more potent and offer more chemical stability. All of these have been shown to have clinical efficacy, but the semi-synthetic compounds are more likely to lead to resistance arising



Pyrethrin I

Fig. 18.18

because of their persistence. Pyrethrum is mostly considered to be harmless to humans and animals, and may be used as a spray, lotion or powder, or fumigant. Pyrethroids are much less toxic to humans than synthetic insecticides, but care should be taken as they can cause irritation or allergic reactions.

QUASSIA WOOD, *PICRASMA EXCELSA* (SW.) PLANCH AND *QUASSIA AMARA* L.

Picrasma excelsa and other species, and *Quassia amara* (Simaroubaceae) are both known as quassia or bitter wood. Jamaica quassia is *P. excelsa*, Surinam quassia is *Q. amara* and Japanese quassia is *P. ailanthoides* Planch. The wood occurs in commerce as logs, chips or shredded; it is whitish, becoming yellow on exposure to the air.

Constituents

Quassia contains quassinoids such as quassin, isoquassin (= picrasmin), neoquassin, 18-hydroxyquassin, quassinol, quassialactol, quassimarin and similikalactones, nigaki lactones A–N and nigaki hemiacetals A–F, and picrasins B, H, I, J depending on the species. *P. excelsa* and *Q. amara* also contain carboline alkaloids including canthin-6-one and various methoxy and hydroxy derivatives, and *P. ailanthoides* contains a series of picrasidine alkaloids.

Therapeutic uses and available evidence

Quassia is an insecticide, anthelmintic, febrifuge and antimalarial, although efficacy in malaria is unproven. It has been used clinically as a fresh infusion to treat head lice in humans, although little evidence for efficacy is available. The quassinoids are responsible for most of the activity; many of them are insecticidal, cytotoxic and amoebicidal both in vitro and in vivo. Quassia has long been used as flavouring in bitter alcoholic and soft drinks, and has been used to stimulate the appetite. Quassia is non-toxic when applied externally, and relatively safe in small doses when ingested.

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The endocrine system

Phytomedicines are often used in the treatment of hormonal disorders, although they are not a substitute for hormone replacement, whether for insulin in diabetes, or natural female and male sex hormones. They do not have a place in the management of thyroid deficiency either, which should be treated with thyroxine. In diabetic patients, many foods and herbs can help to reduce blood glucose levels and may assist in controlling hyperglycaemia in milder cases of non-insulin dependent diabetes. Phytomedicines are much less potent in effect than the sex hormones, but this can be an advantage, as for example with the phytoestrogens. There are several conditions for which phytomedicines may offer at least some symptomatic relief, for example, premenstrual syndrome, which affects around 20–30% of women for up to 2 weeks before the start of menstruation, and the menopause, which affects all women, usually around the age of 51 years. Certain phytomedicines also have beneficial effects in benign prostatic hyperplasia, which is very common in men over 50 years of age and is characterized by a swollen prostate gland, causing frequent or difficult urination.

HYPOGLYCAEMIC AND ANTIDIABETIC HERBS

Many plants and foods lower blood glucose levels by a variety of mechanisms. Although type 1 diabetes (insulin-dependent diabetes mellitus) must be controlled by injections of insulin, type 2 diabetes (non-insulin-dependent diabetes mellitus) responds well to improvements in diet and hypoglycaemic drugs. Phytomedicines have a part to play and are very popular in Asia, where a wide range of herbs is used. Complex carbohydrate preparations, such as guar gum, act by inhibiting glucose absorption from the gut and hence preventing the surge in blood glucose that can occur immediately after a meal. This is a feature of high-fibre diets which are also recommended in diabetes, and such diets also have the advantage of regulating blood cholesterol levels.

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GUAR GUM, *CYAMOPSIS TETRAGONOLOBUS* (L.) TAUBERT (CYAMOPSIDIS SEMEN) EU

Guar gum is obtained from the ground endosperms of the seeds of *Cyamopsis tetragonolobus* (Leguminosae), a plant indigenous to Africa and parts of Asia, producing a yellowish-white flour which can be used to supplement the diet and even made into food items such as pasta. The flour is a source of fibre and used as an adjunct in the treatment of diabetes.

Constituents

These are polysaccharides composed of straight and branched chains of D-galactose and D-mannose polymers.

Therapeutic uses and available evidence

The flour reduces pre- and postprandial glucose levels and is usually given with meals, and may also be of use in lowering blood lipid levels (Butt et al 2007). Like other bulk fibre preparations, it has other clinical effects such as the alleviation of diarrhoea, and it has been advocated as a slimming aid, and this does seem to be justified. It is also used as a thickening and

suspending agent in foods, and as a tablet binder. The usual dose of the powdered gum is 5 g given with each meal. Few side effects have been noted, but patients treated with guar sometimes consider it to be rather unpalatable when made into foods.

GYMNEMA, *GYMNEMA SYLVESTRE* R.BR.

Gymnema sylvestre (Asclepidaceae) grows wild in India, Sri Lanka and tropical Africa. It is a large woody climber with small yellow flowers. The leaves, which are ovate and hairy on both surfaces, have a slightly bitter taste, and if chewed this is followed by a remarkable temporary loss of sensitivity to the taste of sugar and other sweeteners. This unusual property has no relation to the hypoglycaemic effects, although may have originally been the rationale for its traditional use.

Constituents

The leaves and root contain saponin glycosides known collectively as 'gymnemic acid', which consists of a mixture of gymnemic acids, gymnemasins, gymnasides, gymnemosides and their aglycones. Gurmarin, a polypeptide, is responsible for the desensitization of the palate to sweet tastes.

Therapeutic uses and available evidence

The herb is a traditional treatment for diabetes in India but, although widely used, there is insufficient clinical evidence available to recommend this herb as yet. The antihyperglycaemic properties are due to the gymnemic acids and other saponins. Oral administration of a specific standardized extract OSA(R) (1 g/day, 60 days) induced significant increases in circulating insulin and C-peptide, which were associated with a reduction in fasting and post-prandial blood glucose. In vitro measurements using isolated human islets of Langerhans demonstrated direct stimulatory effects of OSA(R) on insulin secretion from human β-cells, consistent with an in vivo mode of action through enhancing insulin secretion (Al-Romaiyan et al 2010). The leaf extract also has hypolipidaemic activity in human patients and animals fed a high-fat diet (Kanetka et al 2007). The usual dose is up to 4 g of leaf daily. Gymnemic acids are well tolerated, but care should be taken when used in conjunction with other antidiabetic agents.

KARELA, *MOMORDICA CHARANTIA* L.

The bitter gourd or bitter melon, karela (*Momordica charantia*, Cucurbitaceae), is grown throughout India, China, Africa and parts of America. It is a slender, climbing shrub with kidney-shaped, lobed leaves. The fruit resembles a cucumber with numerous ridges or warts and soft spines. It has an intensely bitter taste. Both the leaves and fruit are used medicinally.

The plant is widely used in the treatment of diabetes. The fruit is eaten as a vegetable; the leaf may be made into a type of 'bush tea', called 'cerassie'.

Constituents

The plant contains triterpene (cucurbitane-type) glycosides called momordicosides A–L and the goyaglycosides A–H, as well as momordicin, momordicinin and cucurbitanes I, II and III and goyasaponins I, II and III. Proteins and lectins present include α-, β- and γ-momorcharins and momordins a and b.

Therapeutic uses and available evidence

Both the fruit and the leaf have hypoglycaemic effects. The extract causes hypoglycaemia in animals and human diabetic patients, and several clinical studies have confirmed benefits (see review by Grover and Yadav 2004), but a recent Cochrane review (Ooi et al 2010) states that there is insufficient evidence to recommend it for type 2 diabetes mellitus, and that further studies are required to address issues of standardization and the quality control of preparations. It has also been used to treat asthma, skin infections and hypertension (Grover and Yadav 2004). Contraceptive and teratogenic effects have been described in animals, so care should be taken in pregnant women, although cooking the vegetable may well destroy many of the toxins.

PHYTOESTROGENS

There are many plants that contain oestrogenic substances (phytoestrogens), and pharmacological and epidemiological evidence suggests that they act as mild oestrogens or, in certain circumstances, as anti-oestrogens (by binding to oestrogen receptors and preventing occupation by natural oestrogens). They generally have beneficial effects, including chemopreventive activity. As well as the herbs mentioned below, many pulses (which are legumes) contain phytoestrogens, as do linseed and hops. The main chemical types of phytoestrogen are the

isoflavones, coumestans and lignans, and some species of palm even contain similar hormones (e.g. estriol) to those found in the human body. The common occurrence of these substances has implications for men as well as for women, in that the incidence of benign prostatic hyperplasia is lower in men, and menopausal symptoms in women, in societies consuming significant amounts of foods containing these substances in their normal diet. However, a recent case-control study in the UK found no significant associations between phytoestrogen intake and breast cancer risk, although colorectal cancer risk was inversely associated with enterolignan intake in women but not in men (Ward and Kuhnle 2010). Soya phytoestrogen intake may even have a beneficial effect on tumour recurrence (Roberts 2010). As the majority of studies have not involved women with breast cancer and are of short duration, it would be wise for patients with hormone-dependent cancers to avoid taking phytomedicines known to affect hormone levels.

RED CLOVER, *TRIFOLIUM PRATENSE* L.

Red (or pink) clover (Fabaceae) is widely distributed throughout Europe, naturalized in North America and found in many other parts of the world. The flower heads are ovoid, red or pinkish purple, about 2–3 cm in diameter, composed of numerous individual, keeled flowers. The leaflets are trefoil, often with a whitish crescent in the centre. Both the leaves and isolated isoflavones are used medicinally.

Constituents

The major actives are phytoestrogens of two types: the isoflavones genistein (Fig. 19.1), afrormosin, biochanin A, daidzein, formononetin, pratensein, calyconin, pseudobaptigenin, orobol, irilone and

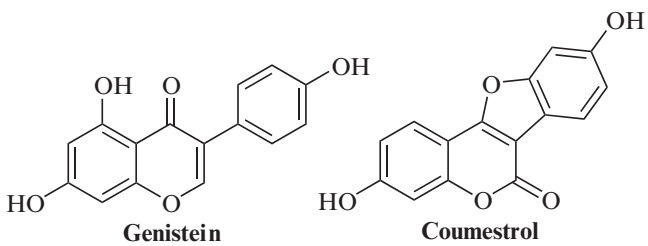


Fig. 19.1

trifoside, and their glycoside conjugates; and the coumestans coumestrol (Fig. 19.1) and medicagol.

Therapeutic uses and available evidence

Red clover was traditionally used for skin complaints such as psoriasis and eczema, and as an expectorant in coughs and bronchial conditions. However, it has recently been used more as a source of the isoflavones, for a natural method of hormone replacement therapy (for review, see Sabudak and Guler 2009). The isoflavones are oestrogenic in animals but the clinical use for menopausal women has not yet been well supported by clinical studies, except for a marginally significant effect for treating hot flushes in menopausal women (Coon et al 2007). Biochanin A inhibits metabolic activation of the carcinogen benzo(a)pyrene in a mammalian cell culture, suggesting chemopreventive properties. Red clover extracts also inhibit cytochrome P450 3A4 in vitro, which supports such a use. Red clover is considered safe.

SOYA, *GLYCINE* MAX (L.) MERR.

Soya (Fabaceae) is a low-growing, typically leguminous crop plant, producing white or yellow beans. It is an important item of diet in many countries and is used in many ways. For example 'soya milk' is used as a substitute for animal milk in allergic people (especially babies), and can be made into yoghurt. The protein is used as a meat substitute and to make tofu, and is fermented into condiments such as 'soy sauce'. The bean sprouts are eaten raw in salads and used in stir-fry dishes; the flour can be made into bread and cakes.

Constituents

Soya contains phytoestrogens of two chemical types: isoflavones including genistein, daidzein and their derivatives, ononin, isoformononetin and others, and coumestans such as coumestrol (especially in the sprouts). There is a fixed oil composed mainly of linoleic and linolenic acids, and phytosterols including β-sitosterol and stigmasterol.

Therapeutic uses and available evidence

Preparations containing the isolated isoflavones are used medicinally. The available epidemiological evidence suggests that a diet high in soya can reduce

menopausal symptoms and prostate enlargement, although clinical trials have not yet proved these benefits.

The isoflavones and coumestans are oestrogenic, and are now being used as a natural form of hormone replacement therapy, although the evidence for this is not conclusive. Dietary inclusion of whole soya foods appears to produce a reduction in some clinical risk factors for osteoporosis, and soy isoflavone supplements moderately decreased the bone resorption marker deoxypyridinoline but did not affect the bone formation markers alkaline phosphatase and serum osteocalcin in menopausal women, although the effects varied between studies (Taku et al 2010).

Cardiovascular disease and lipid profiles in menopausal women have been reported to be improved by consumption of whole soya foods, although results have been conflicting. In an open study of 190 healthy postmenopausal women given 35 mg of soy isoflavones, a reduction in the number of hot flushes was found (Albert et al 2002), but no improvement was seen in women with breast cancer given a beverage containing 90 mg of soy isoflavones. There is still much work to be done on the clinical effects of the isoflavones in soya, but at present it appears that they are beneficial with few adverse effects (for review, see Messina 2010). Opposing advice has been given regarding the safety of dietary phytoestrogen use for women with previous breast cancer. However, as mentioned above, the majority of studies have not been conducted in women with breast cancer and many are of short duration. Soya is considered to be non-toxic.

HORMONAL IMBALANCE IN WOMEN

Although the phytoestrogens can be considered to affect hormone activity, there are other herbal medicines that are considered to have the capacity to regulate hormone levels without necessarily being oestrogenic. Their mechanism of action is generally not known.

BLACK COHOSH, *CIMICIFUGA RACEMOSA* NUTT. (CIMICIFUGAE RACEMOSAE RHIZOME) EU

Black cohosh (syn. *Actaea racemosa* L., Ranunculaceae) is also known as 'squawroot', because of its traditional use for female complaints. In North America, where the plant originates, it was also used to treat snakebite, hence another synonym, 'black snakeroot'. It has also been used for a variety of disparate disorders, including rheumatism, sciatica, chorea and tinnitus. The parts used medicinally are the rhizomes and roots, which are dark brown in colour.

Constituents

The active components of black cohosh are considered to be the triterpene glycosides, such as actein (Fig. 19.2), 27-deoxyactein and several cimicifugosides; the flavonoids may contribute to the activity.

Therapeutic uses and available evidence

Hormonal and antiinflammatory effects have been described for black cohosh and reductions in serum luteinizing hormone concentrations have been documented for methanolic and lipophilic extracts, but there are conflicting data on the oestrogenic activity of the herb. Although there is some evidence from randomized, placebo-controlled clinical trials, it does not consistently demonstrate an effect of black cohosh on menopausal symptoms, including flushes, and further rigorous trials seem warranted (Borrelli and Ernst 2008). Black cohosh use appears safe in women with previous breast cancer (Roberts 2010), but the majority of studies regarding the efficacy of such herbal treatments have not been conducted in women with breast cancer and many are of short duration. Adverse effects are rare, but may include gastrointestinal disturbance and lowering of blood pressure with high doses. It should be avoided in pregnancy and lactation because of insufficient data.

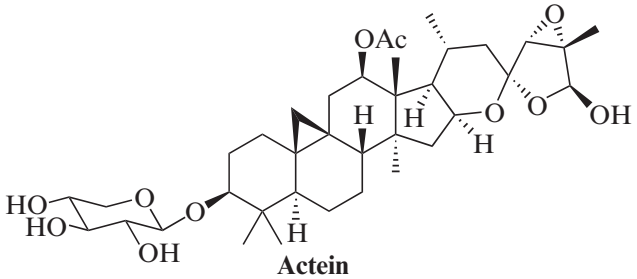


Fig. 19.2

CHASTEBERRY, *VITEX AGNUS-CASTUS* L. (AGNI CASTI FRUCTUS) EU

Vitex agnus-castus (Verbenaceae) is also known by the common names 'chasteberry' and 'chaste tree', but is often referred to simply as 'agnus castus'. It has a history of traditional use for menstrual problems, including premenstrual symptoms and dysmenorrhoea, and also for menopausal complaints. It was considered historically to reduce the libido, especially in men, hence the names 'chasteberry', 'agnus castus' (which means 'chaste lamb') and 'monk's pepper'. *Vitex agnus-castus* is native to the Mediterranean. It is a shrub or small tree, which grows to 1–6 m in height. The fruit (berries) is reddish-black and around 2–4 mm in diameter, and is the part used pharmaceutically.

Constituents

The pharmacologically active components of *Agnus castus* have not yet been clearly established, although the diterpene constituents (e.g. rotundifuran) are likely to be important. Flavonoids, mainly vitexin, casticin, and others, such as kaempferol and quercetagetin, iridoids are also present.

Therapeutic uses and available evidence

Extracts of agnus castus and isolated diterpene constituents display dopamine receptor binding activity in vitro. For example, dopaminergic activity and inhibition of prolactin secretion has been demonstrated in vitro for rotundifuran. Dopaminergic activity is associated with inhibition of prolactin synthesis and release. Modern pharmaceutical uses of agnus castus include menstrual cycle disorders, premenstrual syndrome and mastalgia (cyclical breast pain). There is some evidence from randomized controlled trials to support the effects of proprietary preparations of agnus castus in relieving breast pain in women with mastalgia. Alleviation of symptoms of premenstrual syndrome is also supported by results of randomized controlled trials (for example, Ma et al 2010). In addition, clinical studies provide some evidence to support the effects of agnus castus on lowering prolactin concentrations in hyperprolactinaemia. Other studies have reported that agnus castus does not markedly affect prolactin concentrations in women with normal basal prolactin levels. Although evidence from rigorous randomized controlled trials is lacking for agnus castus in the alleviation of menopausal symptoms, emerging pharmacological evidence supports a role in this context (for review, see Van Die et al 2009).

Agnus castus is generally thought safe, but as with most medicines it is not recommended during pregnancy. It should not be used during lactation as it may suppress milk production; its effects upon neonates are not known.

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is so common in older men that it can almost be considered a normal part of ageing. The symptoms are increased frequency, and difficulty, of micturition (urination). BPH requires a medical diagnosis to eliminate the possibility of prostate cancer, and so self-treatment is only suitable after consultation with a medical practitioner. Severe cases are treated with surgery, which is not always entirely successful, or drug treatment with either specific α-adrenergic-blocking agents or testosterone 5α-reductase inhibitors. α-Blockers relax smooth muscle in BPH and improve urinary flow, but have side effects including drowsiness, syncope and dry mouth. The enzyme 5α-reductase catalyses the conversion of testosterone to the more potent androgen, dihydrotestosterone, and if this is prevented, a reduction in prostate size and consequent improvement in urine flow ensues. Phytotherapy is thought to be as successful (or almost) as synthetic drug treatment, but complete reversal of the enlargement of the prostate is not possible.

NETTLE, *URTICA DIOICA* L. (URTICAE HERBA, RADIX) EU

Urtica dioica (Urticaceae) is commonly known as stinging nettle or simply urtica. Traditionally, it has been used to treat a disparate range of conditions, including uterine haemorrhage, epistaxis, cutaneous eruptions, and nervous and infantile eczema, which have little relation to its modern pharmaceutical uses. It has also been used as supportive therapy in rheumatic ailments. The plant grows to around 60–120 cm in height and has serrated leaves with stinging hairs and bristles. The herb and the roots are the parts used pharmaceutically.

Constituents

The phytochemistry of nettle is well documented, although it is not clear precisely which constituents are responsible for the various activities. Lignans present in the root, including pinoresinol, secoisolariciresinol, dehydrodiconiferyl alcohol and neoolivil, may be important in inhibiting the interaction between sex hormone-binding globulin and 5α-testosterone. Other constituents include lectins, the mixture known as UDA (urtica dioica agglutinin), composed of at least six isolectins, and triterpenes such as oleanolic and ursolic acid derivatives. The leaf contains flavonoids, mainly isorhamnetin, kaempferol and quercetin glycosides, and glycoprotein, with indoles such as histamine and serotonin, betaine, acetylcholine, caffeic, chlorogenic and caffeoylmalic acids.

Therapeutic uses and available evidence

Modern uses of nettle extracts are focused mainly on symptom relief in BPH and adjuvant treatment (i.e. in addition to non-steroidal antiinflammatory drugs) in arthritis and rheumatism. Evidence from in vitro and in vivo (mice) studies measuring sex hormone-binding globulin to human prostate membranes, and by inhibition of proliferation of human prostatic epithelial and stromal cells, suggests that nettle root extracts have beneficial effects on BPH tissue. Several compounds from the roots are also known to be aromatase inhibitors, and there is evidence from some clinical trials to support the use of nettle root extracts for relief of symptoms associated with BPH (for review, see Chrubasik et al 2007). Nettle leaf extracts inhibit the pro-inflammatory transcription factor NF-κB, partially inhibit cyclo-oxygenase and lipoxygenase, and inhibit tumour necrosis factor and interleukin-1β secretion stimulated by lipopolysaccharide. Nettle preparations are generally thought of as safe, with few (if any) adverse events being reported.

PYGEUM BARK, *PRUNUS AFRICANA* (HOOK. F.) KALKM. (PRUNI AFRICANI CORTEX)

The African prune (*Pygeum africanum*, Rosaceae) is a tropical evergreen tree indigenous to central and southern Africa. The use of pygeum bark is becoming more widespread throughout Europe and the USA, and is in danger of becoming scarce due to over-harvesting of the bark.

Constituents

The bark contains sterols and pentacyclic triterpenes, including abietic, oleanolic, ursolic and crataegolic acids, N-butylbenzene-sulfonamide, and esters of ferulic acid.

Therapeutic uses and available evidence

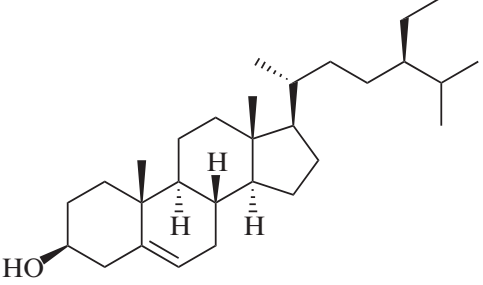
Traditionally used for micturition problems and now for BPH, pygeum extract has antiproliferative and apoptotic effects on proliferative prostate fibroblasts and myofibroblasts, but not on smooth muscle cells (Quiles et al 2010). The compound N-butylbenzene-sulfonamide, isolated from *P. africanum*, is a specific androgen receptor antagonist which inhibits both endogenous prostate serum antigen expression and growth of human prostate cancer cells, but does not interact with oestrogen receptors (Papaioannou et al 2010). Clinical studies have shown the extract to be moderately effective, and it may be a useful treatment option for men with lower urinary symptoms consistent with BPH. However, the studies are small, of short duration, use varied doses and preparations, and rarely report outcomes using standardized validated measures of efficacy, so further work is needed (Wilt et al 2002). Acute and chronic toxicity and mutagenicity tests have shown no adverse effects, and the extract appears to be well-tolerated in men when administered over long periods. It is often used in combination with nettle.

SAW PALMETTO, *SERENOA SERRULATA* HOOK. F. (SABALIS SERRULATAE FRUCTUS) EU

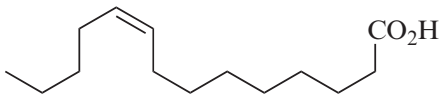
Serenoa serrulata (Arecaceae) is also known as *Serenoa repens* and *Sabal serrulata*, as well as the common name 'saw palmetto'. Saw palmetto is a small 'fan palm', which produces berries with a diameter of 1–2 cm. The fruit (berries) is the part used pharmaceutically. It has been used traditionally for cystitis and sex hormone disorders, including prostatic enlargement. Most commercial saw palmetto comes from the USA.

Constituents

The phytochemistry of saw palmetto is fairly well known, although precisely which components are responsible for the pharmacological effects have yet to be established. Constituents likely to be important include: the fatty acids capric, caprylic, lauric, oleic, myristoleic, palmitic, linoleic and linolenic acids; the monoacyl glycerides 1-monolaurin and 1-monomyristicin; phytosterols such as β-sitosterol, campesterol, stigmasterol, lupeol and cycloartenol (Fig. 19.3). Long-chain alcohols (farnesol, phytol and polyprenolic alcohols) and flavonoids are present, as well as immunostimulant, high-molecular-weight polysaccharides containing galactose, arabinose, mannose, rhamnose and glucuronic acid.



β-Sitosterol



Myristoleic acid

Fig. 19.3

Therapeutic uses and available evidence

Saw palmetto is now mainly used to treat BPH. This is supported by evidence from several randomized controlled trials, which also provided preliminary evidence that extracts (usually liposterolic) achieve improvements similar to those seen with the 5α-reductase inhibitor finasteride (Mantovani et al 2010). However, other studies show no effect and the efficacy is disputed (Barnes 2009; Tacklind et al 2009, Mantovani 2010). Post-marketing surveillance studies suggest that saw palmetto extracts are well tolerated, and comparative clinical studies indicate that they have a more favourable safety profile than finasteride, at least in the short term. Liposterolic and ethanolic extracts of saw palmetto inhibit 5α-reductase (the enzyme which catalyses the conversion of testosterone to 5α-dihydrotestosterone in the prostate) in vitro; other studies have described beneficial effects in animal models of BPH. Spasmolytic activity, which may also contribute to improvements in BPH, has also been documented in vivo (rats) for an ethanolic extract of saw palmetto. In vitro growth arrest of prostate cancer LNCaP, DU145, and PC3 cells (Yang 2007) and in vivo oestrogenic and antiinflammatory activities have been reported for extracts of saw palmetto, and may be due to the high content of β-sitosterol. The antiinflammatory effects may also be due to the presence of the polysaccharides.

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The reproductive tract

Drugs used in hormonal disorders have been covered in Chapter 19. Other drugs that are used in obstetrics, including substances used in childbirth, and genitourinary disorders and erectile dysfunction in men, will be mentioned briefly here.

PHYTOMEDICINES IN CHILDBIRTH

Taking (any) medicine during pregnancy is generally not advisable as safety of the mother and fetus cannot be guaranteed. Raspberry leaf is included here simply because according to folklore it has a widespread use in facilitating childbirth, and it is often recommended that it be taken during pregnancy for this purpose, but the use cannot be recommended as there is little clinical evidence available to demonstrate either safety or efficacy.

ERGOMETRINE EU

Ergometrine (Fig. 20.1) is an alkaloid extracted from ergot (*Claviceps purpurea* Tul.), a parasitic fungus growing on cereals, usually rye. It is used to manage the third stage of labour (in conjunction with oxytocin), and to control postpartum haemorrhage if the placenta has not been completely expelled. It must be used only under the care of a midwife or obstetrician.

RASPBERRY LEAF, *RUBUS IDAEUS* L. (RUBI IDAEI FOLIUM)

Raspberry leaf (*Rubus idaeus*, Rosaceae) 'tea' has been used for centuries to facilitate childbirth, and it is usually recommended that it be drunk freely before and during confinement for maximum benefit. The raspberry shrub is well known and will not be described. It is cultivated in many temperate countries for the fruit.

Constituents

The leaves have not been well investigated, but contain uncharacterized polypeptides and flavonoids, mainly glycosides of kaempferol and quercetin, including rutin.

Therapeutic uses and available evidence

A retrospective observational study on 108 mothers in Australia indicated that a shortening of labour and reduction in medical intervention occurred, with no untoward effects apart from a single case of diarrhoea and anecdotal reports of strong Braxton Hicks contractions. However, a larger, randomized placebo-controlled trial of 192 women by the same authors did not confirm such benefits, although no adverse effects for either mother or baby were noted (Simpson et al 2001). Uterine relaxant effects have been demonstrated in animals (Rojas-Vera et al 2002), and raspberry leaf appears to affect only the pregnant uterus of both rats and humans, with no activity on the non-pregnant uterus. However, no further identification of the active principle(s) has been made and a recent review concludes that in the absence of good clinical data, raspberry leaf cannot be recommended in pregnancy (Holst et al 2009).

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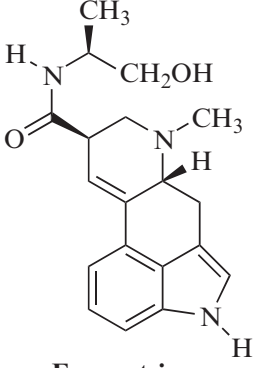


Ergometrine

Fig. 20.1

MALE SEXUAL DYSFUNCTION (IMPOTENCE)

Male impotence (failure to produce a satisfactory or sustainable erection) may result from psychogenic, vascular, neurogenic or endocrine abnormalities (such as diabetes), or drug treatment (e.g. with antihypertensives and antidepressants). It can be treated with either intracavernosal injections of papaverine or alprostadil (prostaglandin E1), intraurethral application (alprostadil) or systemically [sildenafil (Viagra) or apomorphine]. Medical assessment is needed before these drugs are prescribed. Although papaverine is of natural origin, it is only suitable for self-medication after medical diagnosis, but there are several herbal products available, which claim to treat this distressing disorder. The most common are probably epimedium, and yohimbe, a traditional aphrodisiac, and there are others, which are often strange botanical mixtures and usually sold under the description 'Herbal Viagra'. There is no good clinical evidence of efficacy for any of these, although epimedium has some pharmacological actions in common with those of sildenafil (Viagra®), and may have a placebo effect.

EPIMEDIUM BREVICORNUM MAXIM (EPIMEDII HERBA) AND *EPIMEDIUM* SPP.

Epimedium brevicornum Maxim (Berberidaceae) and related species are also known as 'horny goat weed'. The herb was apparently discovered by the Chinese, who noticed that when goats had eaten it, they were eager to mate, and for this reason they called the herb 'yin yang huo', or 'licentious goat plant'. Epimediums are sprawling, attractive, perennial herbs, with cordate leaves and white, cream, pink, yellow or lavender flowers. Although native to Asia and the Mediterranean region, they are widely cultivated. Epimedium has been used for the treatment of erectile dysfunction in Traditional Chinese Medicine for many years. It is also used to ease menopausal symptoms in women and to treat and prevent osteoporosis.

Constituents

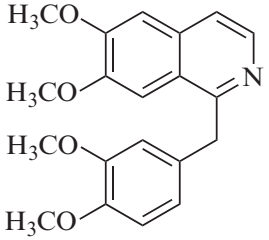
The flavonoids are the active constituents, the most important being icariin and its analogues, with epimedin A, B, and C, and baohuoside I.

Therapeutic uses and available evidence

Icariin has phosphodiesterase type 5 inhibiting effects (the mechanism of action of sildenafil) and may also have neurotrophic effects (Zeng et al 2010, Ma et al 2011). A study of the effects of icariin administered daily to cavernous nerve-injured rats found that the ratio of intracavernous pressure to arterial pressure was significantly higher compared with control (and also single-dose icariin-treated) animals. The penile tissue of rats treated with icariin showed greater positivity for neuronal nitric oxide synthase and calponin, and cultured pelvic ganglia treated with icariin had significantly greater neurite length (Shindel et al 2010). Icariin is also a bone anabolic agent that may exert its osteogenic effects through the induction of bone morphogenetic protein-2 and NO synthesis, subsequently regulating gene expression and contributing to the induction of osteoblast proliferation and differentiation (Hseih et al 2010).

PAPAVERINE EU

Papaverine (Fig. 20.2) is an alkaloid extracted from the opium poppy (*Papaver somniferum* L.). It is most often used for the treatment of impotence of



Papaverine

Fig. 20.2

neurological or psychogenic origin. As it must be given by intracavernosal injection, it is normally only used as a last resort when less invasive treatments have failed.

YOHIMBE, *PAUSINYSTALIA JOHIMBE* (K. SCHUM.) PIERRE

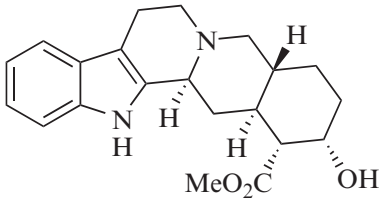
Yohimbe bark (Rubiaceae) occurs as flat or slightly quilled pieces, often covered with lichen.

Constituents

The bioactive constituents are indole alkaloids, the major one being yohimbine, together with α- and β-yohimbane, pseudoyohimbine and coryantheine.

Therapeutic uses and available evidence

Yohimbine (Fig. 20.3) is an α-adrenergic blocker and has a wide (but not justified) reputation as a sexual stimulant. It should be used only under the advice of a medical herbalist or physician.



Yohimbine

Fig. 20.3

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The musculoskeletal system

Short-lived and self-limiting inflammatory disorders are not normally treated with phytomedicines, but recently the use of some botanical preparations for chronic inflammatory conditions has become increasingly widespread. The use of analgesic and antiinflammatory drugs such as paracetamol, aspirin and ibuprofen is common for such conditions, but the side effects of these drugs can limit their acceptability. Non-steroidal antiinflammatory drugs (NSAIDs) act mainly via inhibition of cyclooxygenase (COX); enzymes, also known as prostaglandin synthases (PGS). At present three are known, COX-1, COX-2 and COX-3 (a splice variant of COX-1, sometimes referred to as COX-1b). Inhibition of COX-1 (e.g. with aspirin, ibuprofen and diclofenac) reduces levels of the gastroprotective prostaglandins, leading to inflammation of the gastrointestinal lining and even ulceration and bleeding. COX-2, however, is only induced in response to pro-inflammatory cytokines, and is not found in normal tissue (unlike COX-1). It is associated particularly with oedema and the nociceptive and pyretic effects of inflammation. Treatment with inhibitors of COX-2 does not produce such severe gastrointestinal side effects, but there are concerns about their cardiovascular safety. Other targets for treating inflammatory diseases include 5-lipoxygenase (LOX), NF-κB (which is activated in rheumatoid arthritis and other chronic inflammatory conditions), and certain cytokines which inhibit the activity of tumour necrosis factor-α (TNFα). Chronic expression of NO is also associated with various inflammatory conditions, including arthritis.

DRUGS USED IN ARTHRITIS, RHEUMATISM AND MUSCLE PAIN

The classic NSAID, aspirin, was originally developed as a result of studies on salicin, obtained from willow bark (see below and Chapter 15 and – for historical aspects – Chapter 3). Although it was thought at first that the effects of salicin were due only to the hydrolysed product salicylic acid, it is now known that plant antiinflammatory agents tend to have fewer gastrointestinal side effects than salicylates in general. There are also several combination herbal products on the market, for which little clinical data are available, but which are very popular and seem to produce few side effects.

BROMELAIN (ANANASE)

Bromelain is a mixture of proteolytic enzymes extracted from the fruit and stem of the pineapple (*Ananas comosus* L.) and other species of bromeliad (Bromeliaceae). The active constituents are protease-inhibiting enzymes having molecular weights between 5000 and 6000.

Bromelain has been proposed for the treatment of atherosclerosis, dysmenorrhoea, scleroderma, infection and sports injuries. It is antiinflammatory in animal studies and is used clinically to treat bruising, arthritis, joint stiffness and pain, and to improve healing postoperatively, including after dental procedures. It is considered to be an effective alternative to NSAIDs, as shown by a number of clinical trials. A recent study to assess the efficacy of

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bromelain in controlling the oedema and pain after tooth extraction found it to be effective in treating postoperative oedema after third molar surgery (Inchingolo et al 2010). Bromelain, given once daily in acute tendon injury at a dosage of 7 mg/kg for 14 days, promoted healing by stimulating tenocyte proliferation in rats (Aiyegbusi et al 2011). Bromelain is generally well tolerated, but side effects include minor gastrointestinal upsets.

DEVIL'S CLAW, *HARPAGOPHYTUM PROCUMBENS* DC. EX MEISSNER (HARPAGOPHYTI RADIX) EU

Devil's claw (Pedaliaceae) has fairly recently been developed into a successful and relatively well-characterized medicine. The name arises from the claw-like appearance of the fruit. The secondary storage roots are collected in the savannahs of southern Africa (mainly the Kalahari Desert) and, while still fresh, they are cut into small pieces and dried. The main exporters are South Africa and Namibia. Devil's claw was used traditionally as a tonic for 'illnesses of the blood', fever, kidney and bladder problems, during pregnancy and as an obstetric remedy for induction or acceleration of labour, as well as for expelling the retained placenta.

Constituents

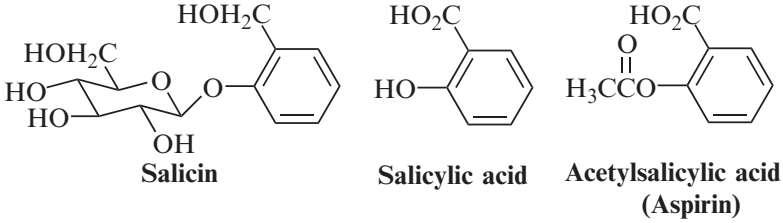
The most important actives are considered to be the bitter iridoids, harpagide and harpagoside (Fig. 21.1), with 8-*O*-*p*-coumaroylharpagide, procumbide, 6′-*O*-*p*-coumaroylprocumbide, pagide and procumboside; the triterpenoids oleanolic and ursolic acids, β-sitosterol and a glycoside harproside. Other compounds present include phenylethyl glycosides such as verbascoside and isoacteoside, polyphenolic acids (caffeic, cinnamic, and chlorogenic acids), and flavonoids such as luteolin and kaempferol. According to the Eur. Ph. the drug must contain ≥1.2% harpagide and harpagoside, expressed as harpagoside.

Therapeutic uses and available evidence

In Europe, a tea (made from a dose of about 1.5 g/day of the powdered drug) has been used for the treatment of dyspeptic disorders such as indigestion and lack of appetite. This effect is due to the presence of bitter glycosides, the iridoids, which are present in large amounts.

Most pharmacological and clinical research has been conducted using standardized extracts for the treatment of rheumatic conditions and lower back pain. Several clinical studies, including some placebo-controlled double-blind trials, demonstrate the superiority of these extracts to placebo in patients with osteoarthritis, non-radicular back pain and other forms of chronic and acute pain. Other studies show their therapeutic equivalence to conventional forms of treatment. Devil's claw is generally well tolerated and appears to be a suitable alternative to NSAIDs, which often have gastrointestinal side effects (for review, see Barnes 2009, Cameron et al 2009).

The mechanism of action is not fully known: fractions of the extract containing the highest concentration of harpagoside inhibited COX-1 and COX-2 activity and greatly inhibited NO production, whereas in contrast, the fraction containing mainly the other iridoids increased COX-2 and did not alter NO and COX-1 activities. A fraction containing mainly cinnamic acid was able to reduce only NO production (Anauate et al 2010). An extract of *Harpagophytum procumbens* showed a significant antiinflammatory effect in the rat adjuvant-induced chronic arthritis model, and harpagoside dose-dependently suppressed the lipopolysaccharide (LPS)-induced production of inflammatory cytokines (IL-1β, IL-6, and TNF-α) in mouse macrophage cells (Inaba et al 2010). These demonstrate that harpagoside is probably the main active constituent



Salicin **Salicylic acid** **Acetylsalicylic acid (Aspirin)**

Fig. 21.1

responsible for the effect of devil's claw, but that other components from the crude extract can antagonize or increase the synthesis of inflammatory mediators. In summary, both the pharmacological mechanism and the compounds responsible for this activity have to be investigated further, and by in vivo methods. There are implications for the production methods for preparing devil's claw extracts, and a recent study of the antiinflammatory activity of various commercial products has demonstrated that there is a great difference in their composition, and concludes that the harpagoside content is not a reliable method of predicting the therapeutic efficacy (Ouitas and Heard 2010). Extracts of devil's claw are generally well tolerated but should not be used for patients with gastric or duodenal ulceration. The aqueous extract possesses spasmogenic, uterotonic action on rat uterine muscles (Mahomed and Ojewole 2009), leading credence to the folkloric obstetric uses, but suggesting that it should be avoided in pregnant women. Side effects include minor gastrointestinal upsets.

ROSEHIP, *ROSA CANINA* L. (ROSAE PSEUDOFRUCTUS; ALSO KNOWN AS ROSAE FRUCTUS OR ROSAE PSEUDOFRUCTUS CUM FRUCTIBUS)

The fruits of the wild or dog rose, *Rosa canina* (Rosaceae) are known as rosehips, and are botanically 'pseudofruits', composed of achenes enclosed in a fleshy receptacle or hypanthium. The trichomes found inside rose hips are irritant and are often removed before powdering the fruit. There are several types of rosehip preparation available: rosehip and seed (the ripe pseudofruits, including the seed); rosehip (the ripe seed receptacle, freed from seed and attached trichomes), and rosehip seed (the ripe, dried seed). The whole pseudofruit, i.e. rosehip with seed, is most commonly used and widely investigated.

Constituents

Antiinflammatory constituents isolated from rosehip extracts include the triterpene acids, oleanolic, betulinic and ursolic acids; oleic, linoleic and alpha-linolenic acids, and a series of galactolipids which are thought to be a major contributor to the effects (Chrubasik et al 2008b).

Therapeutic uses and available evidence

Traditionally, rose hips were used as a source of vitamin C and were made into syrups for that purpose, but modern use is now focused on their antiinflammatory effects (for review, see Chrubasik et al 2008a). In a pilot surveillance study which included 152 patients with acute exacerbations of chronic pain, mainly of the lower back and knee, patients were recommended rose hip and seed powder at a dose providing up to 3 mg of galactolipid/day for up to 54 weeks. Multivariate analysis suggested an appreciable overall improvement, irrespective of type of pain, and this was reflected for most of the individual measures. There were no serious adverse events (Chrubasik et al 2008b). In a recent double-blind placebo-controlled trial of 89 patients with rheumatoid arthritis, treatment with encapsulated rose-hip powder 5 g daily for 6 months suggested that patients with rheumatoid arthritis may benefit from additional treatment with rose hip (Willich et al 2010). A study comparing powdered rose hip with and without the seeds found that extracts derived from rose hip without fruits were more effective in assays carried out for inhibition of COX-1, COX-2 and 5-LOX-mediated leukotriene B(4) formation, as well as for antioxidant capacity (Wenzig et al 2008). Extracts of rosehips have displayed potent antiinflammatory and antinociceptive activities in several in vivo experimental models (Deliorman Orhan et al 2007, but the mechanism of action and the active constituents are still not fully known. Bioassay-guided fractionation of rosehip powder yielded the triterpene acids, oleanolic acid and ursolic acid, as inhibitors of lipopolysaccharide induced interleukin-6 release (Saaby et al 2011), but these are ubiquitous compounds and may only play a part in the overall activity.

TURMERIC, *CURCUMA DOMESTICA* VAL. (CURCUMAE DOMESTICAE RHIZOMA) EU

The rhizomes of turmeric (syn. *C. longa* L., Zingiberaceae) are imported as a ready-prepared and ground, dark yellow powder with a characteristic taste and odour. The distinctive colour and presence of starch grains (as both simple and compound grains) and cork make the microscopic identification of the drug relatively straightforward. Turmeric is used in religious ceremonies by Hindus and Buddhists. It is important in the preparation of curry powders and

is increasingly being used as a colouring agent because of the increased use of natural ingredients in foods. A related species is Javanese turmeric (*Curcuma xanthorrhiza* Roxb., Curcumae xanthorrhizae rhizoma; Eur. Ph.), which is mostly used for dyspepsia and other gastrointestinal problems.

Constituents

Three classes of compounds are particularly important: the curcuminoids – the mixture known as curcumin (Fig. 21.2) – consisting of several phenolic diarylheptanoids including curcumin, monodemethoxycurcumin and bisdemethoxycurcumin; an essential oil (about 3–5%), containing about 60% sesquiterpene ketones (turmerones), including arturmerone, α-atlantone, zingberene, with borneol, α-phellandrene, eugenol and others; and polysaccharides such as glycans, the ukonans A–D.

Therapeutic uses and available evidence

Turmeric is becoming increasingly popular in the West, as an antiinflammatory and antihepatotoxic agent (see also Chapter 14, Gastrointestinal and biliary system). It is also widely used in Ayurveda and Chinese medicine as an antiinflammatory, digestive, blood purifier, antiseptic and general tonic. It is given internally and also applied externally to wounds and insect bites. Most of the actions are attributable to the curcuminoids, although some of the essential oil components are also antiinflammatory. The efficacy of curcumin and its regulation of multiple targets, as well as its safety for human use, means that turmeric has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease and many other inflammatory illnesses (for review, see Zhou et al 2011). Antiinflammatory properties have been documented in numerous pharmacological models, and the use of turmeric seems promising, despite the limited number of clinical studies and poor bioavailability (for review, see Henrotin et al 2010). Curcumin has been studied as an anticancer drug and inhibits iNOS (inducible nitric oxide synthase) in both in vitro and in vivo mouse models via a mechanism involving the pro-inflammatory transcription factor NF-κB. It has also been shown to inhibit the activation of another transcription factor (AP-1), indicating that curcumin may be a non-specific inhibitor of NF-κB. Reports also indicate cyclo-oxygenase inhibition and free radical scavenging ability as potential targets (for review, see Epstein et al 2010). Immunostimulant activity, due to the polysaccharide fraction, has been shown, and anti-asthmatic effects have been noted, together with antimutagenic and anticarcinogenic effects. It is the subject of much current research but clinical evidence is urgently needed. Turmeric is well tolerated.

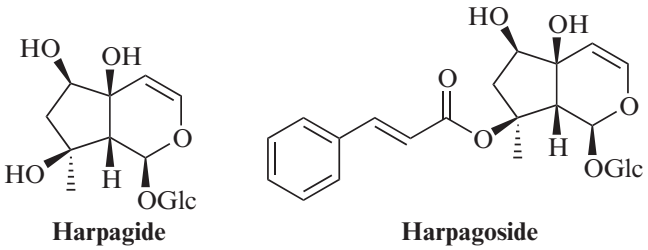


Fig. 21.2

WILLOW BARK, *SALIX* SPP. (SALICIS CORTEX) EU

Salix spp., including *S. purpurea* L., S. *fragilis* L., S. *daphnoides* Vill. and S. *alba* L. (Salicaceae), are the source of the drug 'willow bark'. They are trees and shrubs common in alpine ecosystems, flooded areas and along the margins of streams. Willow bark is a European phytomedicine with a long tradition of use for chronic forms of pain, rheumatoid diseases, fever and headache. As is well known, one of its main compounds, salicin, served as a lead molecule for the development of aspirin (acetylsalicylic acid).

Constituents

Phenolic glycosides, including salicin (Fig. 21.3), phenolic acids, tannins (mainly dimeric and polymeric procyanidins) and flavonoids are the most prominent groups of compounds. The most commonly used willow bark dry extract has a salicin content of 15–18%.

Very few pharmacological studies of individual compounds from willow bark (and their metabolites)

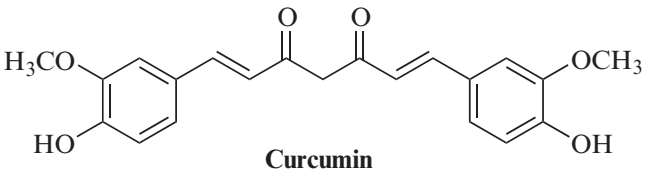


Fig. 21.3

have been conducted. The extract, however, exerts effects on several pro-inflammatory targets, including both isoforms of cyclo-oxygenase and, recently, willow bark water extract STW 33–1 has been shown to produce a significant inhibition of TNFα and NF-κB in activated monocytes (Bonaterra et al 2010).

Therapeutic uses and available evidence

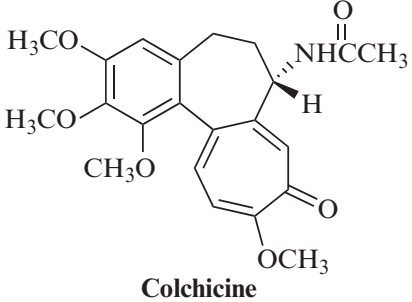
Willow bark has been studied clinically. The effectiveness of an extract of willow bark (which is licensed as a medicine in Germany) has been shown to be superior to placebo for osteoarthritis and lower back pain, and with fewer side effects than for example aspirin (for review, see Vlachlojannis et al 2009). However, further more stringent clinical and mechanistic studies are needed. In very high doses, the side effects of salicylates may be encountered, although these are rarely seen at therapeutic levels of the extract. In general, the effective dose contains lower amounts of salicylate than would be expected by calculation, and a form of synergy is thought to be operating within the extract.

DRUGS USED IN GOUT

Gout is a very painful, localized inflammation of the joints (particularly those of the thumb and big toe) caused by hyperuricaemia and the consequent formation of needle-like crystals of uric acid in the joint. For prevention, the xanthine oxidase inhibitor allopurinol is the drug of choice, but an alternative is sulfinpyrazone, which increases excretion of uric acid. Prophylactic treatment should never be initiated during an acute attack as it may prolong it. Acute gout is normally treated with indomethacin or other NSAIDs (but not aspirin), but, if inappropriate, colchicine can be used.

COLCHICINE EU

Colchine (Fig. 21.4) is a pure alkaloid extracted from the corms and flowers of *Colchicum autumnale* L., the autumn crocus or meadow saffron (Colchicaceae, formerly Liliaceae). The plant grows from bulbs in meadows throughout Europe and North Africa, typically appearing during the autumn, with the fruit developing over winter and being dispersed prior to the first mowing of the meadows. The leaves and the fruit appear during spring. The plant extract



Colchicine

Fig. 21.4

is not used because colchicine is highly toxic and the dose must be rigorously controlled.

Colchicine is used in the acute phase of gout, particularly when NSAIDs are either ineffective or contraindicated (for review, see Schlesinger et al 2009). Colchicine is occasionally also used as prophylaxis for Mediterranean familial fever. It is an important tool for biochemical research, as an inhibitor of the separation of the chromosomes during mitosis (e.g. used in breeding experiments to produce polyploid organisms). Colchicine causes gastrointestinal upsets such as nausea, vomiting, abdominal pain and diarrhoea. The dose is 1 mg initially, followed by increments of 500 μg every 2–3 hours until relief is obtained, to a maximum of 6 mg. The course should not be repeated within 3 days.

TOPICAL ANTI-INFLAMMATORY AGENTS

Most topical antirheumatics are rubifacients, which act by counter-irritation. They are used for localized pain or when systemic drugs are not appropriate. Many contain salicylates, and capsaicin is used for severe pain (e.g. with shingles). They should not be used in children, pregnant or breastfeeding women or with occlusive dressings. Arnica is also widely employed, despite little clinical evidence to support its use.

ARNICA, *ARNICA MONTANA* L. (ARNICAE FLOS) EU

Arnica (Asteraceae) is widely used in many European countries, including the UK. The flower heads are the part used, and, as A. *montana* is protected, other species are being investigated as substitutes. Extracts and tinctures are applied topically, for bruising, sprains, swellings and inflammation, usually in the form of a cream or gel.

Constituents

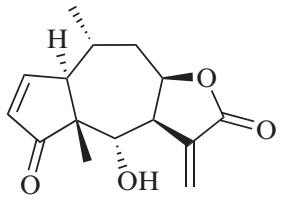
Arnica species are rich in sesquiterpene lactones of the pseudoguianolide type. The most abundant sesquiterpene lactone in *A. montana* is helenalin (Fig. 21.5), with 11α,13-dihydrohelenalin. Flavonoids, including quercetin and kaempferol derivatives, some coumarins and an essential oil are the other groups of natural products found typically in the flower heads of arnica.

Therapeutic uses and available evidence

Extracts of arnica and the pure sesquiterpene lactones with an exocyclic methylene group (e.g. helenalin) have been shown to exert antiinflammatory effects in vivo in animal models, although few clinical studies have been carried out. A randomised, double-blind study in 204 patients with active osteoarthritis of the hands, carried out to compare ibuprofen gel (5%) with arnica gel (50 g tincture/100 g, drug extract ratio 1:20), found that there were no differences in pain relief and hand function after 21 days' treatment between the two groups. Adverse events were reported by five patients (4.8%) on arnica, slightly lower than the ibuprofen group (Widrig et al 2007).

However, a recent trial conducted in 53 subjects who were carrying out eccentric calf exercises found that rather than decreasing leg pain, arnica increased leg pain 24 hours after exercise (Adkison et al 2010). However, this effect did not extend to the 48-hour measurement, and it is not clear how this model relates to most of the clinical situations in which arnica is used. There was no difference in muscle tenderness or ankle range of motion.

Helenalin is well known for its in vitro effects on several transcription factors, including NF-κB and NF-AT. Arnica preparations also suppress matrix metalloproteinase-1 (MMP1) and MMP13 mRNA levels in articular chondrocytes at low concentrations, possibly due to inhibition of DNA binding of the transcription factors AP-1 and NF-kappaB (Jäger et al 2009). The cytotoxicity of the sesquiterpene lactones is well documented, and allergic reactions may occur. Arnica is used externally, except in homoeopathic preparations, but the sesquiterpene lactones have been shown to be absorbed through the skin (Tekko et al 2006).



Helenalin

Fig. 21.5

CAPSAICIN

Capsaicin is the pungent oleo-resin of the fruit of the chilli pepper (*Capsicum frutescens* L., and some varieties of *C. annuum* L., Solanaceae), also known as capsicum, cayenne, or hot. Green and red (or bell) peppers and paprika are produced by milder varieties. The plant is indigenous to tropical America and Africa, but is widely cultivated.

Constituents

Capsaicin itself is 8-methyl-*N*-vanillyl-non-6-enamide; other capsaicinoids such as dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin are present in the natural product. These are esters of vanillyl amine with C_8-C_{13} fatty acids.

Therapeutic uses and available evidence

Capsaicin acts on vanilloid receptors, causing inflammation, but it also desensitizes sensory nerve endings to pain stimulation by depleting the neuropeptide Substance P from local C-type nerve fibres. It is used as a local analgesic in the treatment of postherpetic neuralgia, diabetic neuropathy, osteoarthritis and for pruritus (Papoiu and Yosipovitch 2010). In the management of intractable neuropathic pain, it may provide a degree of pain relief to some patients (Derry et al 2009). Capsaicin has long been used in cough and cold remedies, and recent findings that the vanilloid 1 (TRPV1) receptor is a sensor of airway irritation and initiator of the cough reflex (Geppetti et al 2010) may provide a rationale for that usage.

For external use, capsaicin is normally formulated as a cream containing 0.025%, 0.075% or 0.75%. Capsaicin can produce severe irritation. It causes burning on initial application and should not be applied near the eyes, mucous membranes or to broken skin. It should be avoided in children and pregnant or breastfeeding women.

WINTERGREEN OIL, *GAULTHERIA PROCUMBENS* L., *BETULA LENTA* L.

Wintergreen oil is now most often obtained from *Betula lenta* (Betulaceae) rather than *Gaultheria procumbens* (Ericaceae), although both have similar

compositions. It has a characteristic odour of methyl salicylate.

Constituents

The oil contains methyl salicylate (about 98%), which is produced by enzymatic hydrolysis of phenolic glycosides during maceration and steam distillation.

Therapeutic uses and available evidence

Methyl salicylate is antiinflammatory and antirheumatic. Oil of wintergreen is used mainly in the form of an ointment or liniment for rheumatism, sprains, sciatica, neuralgia and all kinds of muscular pain. Methyl salicylate can cause irritation. It should not be applied near the eyes, mucous membranes or to broken skin, and should be avoided in children and pregnant or breastfeeding women.

NOCTURNAL LEG CRAMPS

Night cramps are common in elderly people, and particularly in patients with liver disease such as cirrhosis.

QUININE EU

Quinine is isolated from the bark of *Cinchona* spp. Quinine salts can be effective in reducing their incidence, but should be avoided for routine use in the management of muscle cramps because of their potential for cardiac toxicity. However, in select patients they can be considered once potential side effects are taken into account. It has been recommended that quinine should be used more in patients with cirrhosis, subject to further investigations (Corbani et al 2008). Quinine salts are used in doses of 200–300 mg at bedtime, in ambulatory patients. For further information on quinine, including the structure, see Chapter 18.

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The skin

Inflammatory and infectious skin diseases have a high prevalence in both developing and developed countries. Anti-infective preparations have been covered separately in Chapter 18. It is in the areas of dry and itchy skin, inflammation and wound healing, that medicinal plants have an important place.

DRY/ITCHY SKIN CONDITIONS AND ECZEMA

Dry and scaly skin conditions are very common and can arise from many causes. Diagnosis should be carried out initially by a medical practitioner in order to exclude infection, infestation or other serious disorders. Emollients, such as oil-based preparations based on arachis oil, or oat extracts, are usually the first line of treatment. Plant extracts are often incorporated into these preparations and can be very useful.

ARACHIS OIL (ARACHIDIS OLEUM RAFFINATUM) EU

Arachis oil (also known as groundnut or peanut oil) is expressed from *Arachis hypogaea* L. (Fabaceae). It is a fixed oil consisting mainly of glycerides of oleic and linoleic acids. It is an ingredient of emollient creams and bath oils. Peanuts are dangerously allergenic to some individuals, and the oil should be avoided in these patients as a precaution.

OATS, *AVENA SATIVA* L.

Oats (*Avena sativa*, Graminae) are a widely distributed cereal crop. The seeds, with the husks removed, are crushed to form a coarse powder, which is creamy white in colour.

Constituents

Oats contain proteins (prolamines known as avenin, avenalin and gliadin), polyphenols known as avenanthramides, starch and soluble polysaccharides (mainly β-glucans and arabinogalactans), saponin glycosides including avenacosides A and B, and soyasaponin I. The fatty oil is composed of phytosterols including cholesterol, β-sitosterol and Δ^5-avenasterol, avenoleic, oleic, ricinoleic and linoleic acids and vitamin E.

Therapeutic uses and available evidence

Oats are externally emollient, and a colloidal fraction is used in bath preparations for eczema, and itchy or dry skin, often with success, especially if used regularly over a long period. Cells treated with avenanthramides showed a significant inhibition of TNF-alpha-induced NF-kappaB activity and subsequent reduction of interleukin-8 (IL-8) release. Topical application of avenanthramides mitigated inflammation in murine models of contact hypersensitivity and neurogenic inflammation and reduced pruritogen-induced scratching in a murine itch model. Avenanthramides are thus potent anti-inflammatory agents that appear to mediate the anti-irritant effects of oats (Sur et al 2008). The many

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clinical properties of colloidal oatmeal derive from its variety of chemical constituents: the starches and beta-glucans are responsible for the protective and water-holding functions of oat and the presence of phenolics confers antioxidant and antiinflammatory activity. Some of the oat phenols are also strong ultraviolet absorbers and the cleansing activity of oat is mostly due to saponins (Kurtz and Wallo 2007). Together, these make colloidal oatmeal a cleanser, moisturizer, buffer, as well as a soothing and protective antiinflammatory agent (for review, see Cerio et al 2010).

Oat tinctures are also taken internally for their reputed sedative activity, but this has not yet been proven. Ingestion of oats lowers cholesterol levels; an effect attributed to the saponins and polysaccharides.

INFLAMMATORY SKIN CONDITIONS

Allergic reactions, psoriasis, burns, bruising and general inflammation of skin are common. Severe cases are treated with corticosteroids as well as emollient preparations, ideally under medical supervision. However, minor disorders respond well to phytotherapy, with soothing and antiinflammatory herbal products, as outlined below.

ALOE VERA, *ALOE BARBADENSIS* MILL. [SYN. *ALOE VERA* (L.) BURM. F.]

The name 'aloe vera' is usually applied to the gel obtained from the centre of the fleshy leaves of various species of aloe, to differentiate from the anthraquinone-rich exudate or 'aloes', which is used as a purgative. The botanical nomenclature of the genus *Aloe* (Asphodeliaceae) is complex. The succulent, non-fibrous leaves are about 30–40 cm long, up to 5 cm in diameter and occur in a terminal, sessile rosette. It is common practice in the tropics to use the gel and the heated leaves for burns and other inflammatory skin conditions. Aloe vera is added to shampoo, skin creams, 'after sun' preparations (and even washing powder), but normally in concentrations too low to have any therapeutic effect.

Constituents

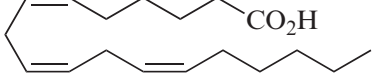
An ill-defined extract of the fleshy leaves, obtained by cutting open and scraping out the gel, is used in the preparation of externally used products, especially cosmetics. It contains polysaccharides consisting mainly of glucomannans, glycoproteins such as the aloctins, enzymes such as carboxypeptidases and variable amounts of anthraquinone glycosides.

Therapeutic uses and available evidence

Aloe vera gel is used mainly in the form of the pure gel, applied as a lotion. It may be stabilized and a preservative added for this purpose. For dermatological preparations, there is some evidence for antibacterial, antiinflammatory, emollient and moisturizing effects. The polysaccharides are important as soothing and immunostimulating agents. Some of the glycoproteins have similar effects, while the anthraquinone derivatives are antibacterial. Enzymes extracted from aloe vera gel have been shown to be analgesic and inhibit thermal damage and vascular permeability in mice. The fresh leaf pulp is antioxidant and induces carcinogen-metabolizing phase I enzymes. The gel has been reported to be effective in the treatment of stomach and aphthous (mouth) ulcers. Although few good clinical studies are available, aloe vera gel seems to be helpful in the treatment of burns and to aid wound healing (for review, see Maenthaisong et al 2007). Aloe vera cream was found to be at least as effective as 0.1% triamcinolone acetonide in reducing the clinical symptoms of psoriasis in a recent study (Choonhakarn et al 2010), and in UV-induced erythema, aloe vera gel (97.5%) displayed some antiinflammatory effects superior to those of 1% hydrocortisone in placebo gel (Reuter et al 2008), supporting its use as an after-sun treatment and post-radiotherapy emollient.

EVENING PRIMROSE OIL, *OENOTHERA BIENNIS* L. (OENOTHERA BIENNIS OLEUM) AND OTHER SPP.

Oenothera spp. (Onagraceae) are common ornamentals, the use of which, in Western phytomedicine, was inspired by that of the indigenous North American Indians. It is now of the seed oil that is used in the treatment of atopic eczema. The plant is a medium or tall hairy perennial with alternate, lanceolate leaves and relatively large yellow, four-petalled flowers, developing into long elongated capsules containing the seeds from which the oil is extracted.



γ-Linolenic acid

Fig. 22.1

Constituents

The seed oil contains about 70% *cis*-linoleic acid and about 9% *cis*-γ-linolenic acid (Fig. 22.1).

Therapeutic uses and available evidence

The fatty oil has been extensively investigated, and its therapeutic benefits ascribed mainly to the γ-linolenic acid content. It is taken internally as well as applied externally. Supplementation with omega-6 essential fatty acids (omega-6 EFAs) is of potential interest in the treatment of atopic dermatitis since patients with atopic dermatitis have been reported to have imbalances in EFA levels. EFAs play a vital role in skin structure and physiology, and deficiency replicates the symptoms of atopic dermatitis. To date, most studies of EFA supplementation in atopic dermatitis have produced conflicting results, although a systematic review has concluded that evening primrose oil has a simultaneous, beneficial effect on itching, crusting, oedema and redness that becomes apparent between 4 and 8 weeks after treatment is initiated. This effect is said to be reduced in association with increasing frequency of potent steroid use (Morse and Clough 2006). The main indications for which clinical evidence exists are: atopic eczema (especially in infants), mastalgia, rheumatoid arthritis and premenstrual syndrome, although the evidence of efficacy is equivocal. Evening primrose oil is usually taken in conjunction with vitamin E to prevent oxidation.

Note: The seed oil of *Borago officinalis* L. (borage, Boraginaceae), also known as Star Flower oil, is used in a similar way to evening primrose oil, but contains 2–3 times more γ-linolenic acid. It seems to provide some benefit to patients with atopic eczema (Foster et al 2010).

MARIGOLD, *CALENDULA OFFICINALIS* L. (CALENDULAE FLOS) EU

Calendula officinalis (Scotch or 'pot') marigold is one of the best known medicinal plants of Europe and has a long tradition of pharmaceutical use. Its origin is unclear and it has been cultivated for many centuries. Consequently, many varieties exist and its usage as an ornamental has increased the botanical variance in the species. The flower heads are relatively large, with a diameter of up to 5 cm, and yellow-orange. Some varieties have both ligulate (tongue-shaped) and radiate florets, others have only the ligulate type. The Eur. Ph. (European Pharmacopoeia) requires that only flower heads exclusively containing ligulate florets should be used.

Constituents

Marigold flowerheads contain saponins based on oleanolic acid, including calendasaponins A, B, C and D, and triterpene pentacyclic alcohols such as faradol, arnidiol, erythrodiol, calenduladiol, heliantriols A1, B0, B1 and B2, taraxasterol, lupeol and ursatriol. It also contains flavonoids, including hyperoside and rutin; sesquiterpene and ionone glycosides such as officinosides A, B, C and D, loliolide and arvoside A; a volatile oil and polysaccharides PS-I, -II and -III; and chlorogenic acid.

Therapeutic uses and available evidence

Pharmaceutical uses include inflammatory skin conditions such as topical application for wound healing and after radiotherapy. The flower heads and extracts from them are well known for their antiinflammatory properties, which are mainly due to the lipophilic triterpene alcohols, notably the esters of faradiol. These were demonstrated using in vitro models such as phorbol ester induced mouse ear oedema or croton oil induced irritation. Marigold extract prevented UVB irradiation-induced GSH depletion in the skin of hairless mice after oral administration and increased gelatinase activity, which may be beneficial for skin healing and procollagen synthesis (Fonseca et al 2010). Both oral and topical application of *Calendula* flower extract improved healing of excision wounds in rats and reduced the time needed for re-epithelization (Preethi and Kuttan 2009). Extracts stimulated proliferation and migration of fibroblasts at low concentrations (Fronza et al 2009), again supporting its use in wound healing, while the essential oil exerts (in vitro) antibacterial and antifungal effects. Immunostimulant effects have been reported for polysaccharide fractions. Few clinical studies are available to further validate these pharmacological data, although some preliminary studies indicate efficacy.

WITCH HAZEL, *HAMAMELIS VIRGINIANA* L. (HAMAMELIS FOLIUM, AND HAMAMELIS FOLIUM ET CORTEX) EU

Witch hazel (*Hamamelis virginiana* L., Hamamelidaceae) is indigenous to North America and Canada. The leaves are broadly oval, up to 15 cm long, 7 cm broad, the margin dentate or crenate, the apex acute and the base asymmetrically cordate. The distilled extract, known simply as 'witch hazel', is used as an astringent in skin and eye inflammation.

Constituents

The leaves and bark contain tannins, composed mainly of gallotannins with some condensed catechins and proanthocyanins. These include 'hamamelitannin' which is a mixture of related tannins, including galloylhamameloses and flavonoids.

Therapeutic uses and available evidence

Witch hazel is widely used for the treatment of haemorrhoids, bruises, skin irritation, spots and blemishes and redness of the eye. Hamamelitannin inhibits TNF-mediated endothelial cell death without altering TNF-induced upregulation of endothelial adhesiveness (Habtemariam 2002), which may explain the anti-haemorrhagic use. The proanthocyanidins, gallotannins and gallates are highly active as free radical scavengers. Witch hazel phenolics protected red blood cells from free radical-induced haemolysis and were mildly cytotoxic to 3T3 fibroblasts and HaCat keratinocytes; they also inhibited the proliferation of tumoral SK-Mel 28 melanoma cells at lower concentrations than grape and pine procyanidins (Touriño et al 2008).

Antiviral activity against *Herpes* viruses has been shown, and several clinical studies have demonstrated efficacy of topically applied witch hazel in inflammatory conditions, including UV-irradiated burning and atopic dermatitis (Hughes-Formella et al 2002). An observational study in children (age 27 days to 11 years) with minor skin injuries, diaper dermatitis, or localized inflammation of skin found hamamelis ointment to be as effective as dexpanthenol, and concluded that hamamelis ointment is an effective and safe treatment for certain skin disorders in children up to the age of 11 years (Wolff and Kieser 2007). However, a review of the literature of hamamelis water in women suffering episiotomy pain following childbirth found it to confer no advantage over ice packs (East et al 2007). Witch hazel is used in after-shave lotions and in cosmetic preparations.

WOUND HEALING

CENTELLA ASIATICA (L.) URBAN (CENTELLAE HERBA) EU

Centella asiatica (Apiceae), also known as gotu kola, Indian Pennywort, Brahmi and Manduukaparani, is an important medicinal plant throughout the world. The leaves of this small plant are kidney-shaped (reniform), long-stalked with rounded apices. The pinkish to red flowers are borne in small rounded umbels. It is a native of tropical and subtropical Asia and generally grows along streams, ditches and in low wet areas. As a consequence, this makes the species prone to an exposure to sewerage, so there is a risk of high levels of bacterial and other contaminations (including heavy metals). In Sri Lanka and other countries it is an element of the local cuisine, used as a vegetable or in salads.

Constituents

The triterpenes are generally considered to be the major active components. They are mainly pentacyclic triterpenic acids of the ursane- or oleanane-type, and their glycosides, and include asiatic acid, the asiaticosides, madecassic acid, madecassoside, brahmoside, brahmic acid, brahminoside, thankuniside, isothankuniside, centelloside, madasiatic acid, and the centellasaponins. There are some differences depending on the geographical origin of the plant. Flavonoids based on kaempferol and quercetin are present and there is a small amount of essential oil, with α-humulene, β-caryophyllene and bicyclogermacrene as the main constituents.

Therapeutic uses and available evidence

A wide range of pharmacological effects have been reported, including as a general tonic (see also Chapter 25), the most important being its use in skin conditions, including wound healing, inflammation, psoriasis, keloid and the prevention of stretch marks during pregnancy. Creams containing extracts are applied topically, but the herb is also taken internally for mental disorders, to improve memory, for atherosclerosis and to improve venous

insufficiency and microangiopathy (for review, see Brinkhaus et al 2000).

Despite the lack of clinical studies, pharmacological studies support the use of Centella in skin conditions. Extracts have been shown to significantly increase the wound breaking strength in a rat incision wound model, improving the rate of epithelization and wound contraction (Shetty et al 2006). Different constituents affect the different phases of wound repair: the triterpenes stimulated extracellular matrix accumulation in rat experimental wounds (Coldren et al 2003), whereas asiatic acid stimulated collagen synthesis, and madecassoside increased collagen secretion (Lee et al 2006). Centella has been suggested as a topical anti-psoriatic agent, and extracts have been shown to inhibit keratinocyte replication. The effect was thought to be due to its two constituent triterpenoid glycosides madecassoside and asiaticoside (Sampson et al 2001).

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The eye

Diagnosis of functional disorders of the eye (glaucoma, etc.) should always be carried out by a medical practitioner. The usual precautions when using extracts in the eye (e.g. sterility of eye drops, absence of irritation of solutions, etc.) must also be taken. Simple eye lotions containing mildly astringent and soothing plant products are very popular, especially those containing distilled witch hazel and eyebright herb extracts. However, ophthalmology clearly is not an area where phytotherapy is of wider importance.

INFLAMMATION OF THE EYE

Inflammation may be a result of an allergic reaction, infection or irritation due to dust or particles. Simple irritation of the eye can be treated with an eye lotion or drops, usually containing either extract of witch hazel (see Chapter 22), or the herb eyebright.

EYEBRIGHT, *EUPHRASIA OFFICINALIS* L. AND *E. ROSTKOVIANA* HAYNE (EUPHRASIAE HERBA)

Euphrasia spp. (Scrophulariaceae) have a long history of use in eye disorders, as the name would suggest. The herb is found in meadows and grassy places throughout Europe and temperate Asia. The leaves are opposite near the base and alternate above, about 1 cm long, lanceolate, with four or five teeth on each side; the axillary flowers are two-lipped, small and white, often tinged with purple or with a yellow spot.

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Constituents

Eyebright contains iridoid glycosides, such as aucubin, geniposide, catalpol, luproside, eurostoside, euphroside, veronicoside, verproside and others; lignans, including coniferyl glucosides and eukovoside; tannins; and polyphenolic acids, including gallic, caffeic and ferulic acids.

Therapeutic uses and available evidence

Extract of *Euphrasia* is a traditional remedy for disorders of the eye such as conjunctivitis. Practically no clinical studies have been carried out, but single-dose eye drops containing extracts of the herb were evaluated in a clinical prospective cohort trial for conjunctivitis, and efficacy and tolerability were deemed 'good to very good' by both patients and physicians (Stoss et al 2000). Overall, the evidence for beneficial effects is very limited.

DISTILLED WITCH HAZEL, AQUA HAMAMELIDIS

Distilled witch hazel is prepared by macerating the dormant and partially dried twigs of *Hamamelis virginiana* L.,(Hamamelidaceae). It is often used in eye drops and eye lotions to soothe the eye and clear redness (for further details, see witch hazel, Chapter 22, Skin).

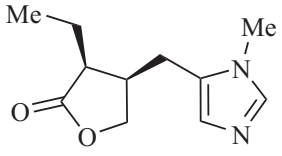
GLAUCOMA

Glaucoma is always treated under medical supervision. It is associated with increased intraocular pressure and can cause blindness if not treated.

Most of the drugs used are synthetic sympathomimetics, such as dipivefrine and brimonidine, β-blockers such as timolol, or prostaglandin analogues, but there is a useful plant-derived miotic (a substance causing constriction of the pupil), the alkaloid, pilocarpine, which is widely used. It reduces intraocular pressure by opening the drainage channels in the trabecular meshwork, which may be affected by a spasm or contraction of the ciliary muscle.

PILOCARPINE

Pilocarpine (Fig. 23.1) is an alkaloid obtained from Jaborandi leaf (*Pilocarpus microphyllus* Stapf. and other species of *Pilocarpus*, Rutaceae). Pilocarpine is a sympathomimetic agent, causing salivation, tachycardia and other effects if taken systemically. Its main use is in ophthalmic preparations as a miotic, in open-angle glaucoma and to contract the pupil after the use of atropine (BNF). It is a prescription-only medicine in most countries.



Pilocarpine

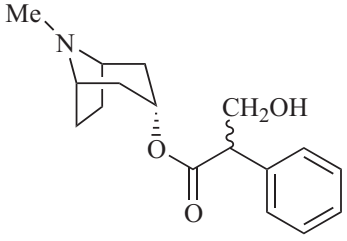
Fig. 23.1

ANTERIOR UVEITIS

Anterior uveitis is an inflammatory disorder of the anterior segment. It is treated (under medical supervision) with atropine or its derivatives, homatropine and tropicamide.

ATROPINE

Atropine (Fig. 23.2) is a tropane alkaloid extracted from deadly nightshade (*Atropa belladonna*, Solanaceae). It is occasionally used as eye drops (0.5%) or ointment (1%) to open the iris for examination or surgical procedures, and to treat anterior uveitis (BNF). See Chapters 4 and 6.



Atropine

Fig. 23.2

Reference

Stoss, M., Michels, C., Peter, E., Beutke, R., Gorter, R.W., 2000. Prospective cohort trial of Euphrasia single-dose eye drops in conjunctivitis. J. Altern. Complement. Med. 6, 499.

British National Formulary. Published biannually by the BMJ Group and the Pharmaceutical Press. See also http://bnf.org/bnf/index.htm.

Ear, nose and orthopharynx

Infections of the ear, nose and throat are treated under medical supervision with antibiotics, but a number of soothing and antiseptic preparations from plant sources are available for use. Decongestants have already been discussed in Chapter 16.

THE EAR

Infections of the ear are treated with either topical or systemic antibiotics. However, the removal of wax from the ear is achieved with the aid of softening agents such as almond, arachis or olive oil (BNF), sometimes followed by ear syringing. For details of arachis oil, see Chapter 22.

ALMOND OIL, *PRUNUS AMYGDALUS* BATSCH (OLEUM AMYGDALI) EU

Almond oil is obtained from the seed of *Prunus amygdalus* Batsch (Rosaceae). It is a fixed oil, also known as sweet almond oil, and consists of triglycerides, mainly triolein and trioleolinolein, together with fatty acids, including palmitic, lauric, myristic and oleic acids.

OLIVE OIL, *OLEA EUROPEA* L. (OLEUM OLIVAE) EU

Olive oil is expressed from the fruits of *Olea europea* L. (Oleaceae). Virgin (or cold-expressed) olive oil has a greenish tinge and is used as a food; refined oil is yellowish. Both have a characteristic odour. Olive oil is a fixed oil containing glycerides of oleic acid (about 70–80%), with smaller amounts of linoleic, palmitic and stearic acid glycerides.

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THE ORTHOPHARNYX

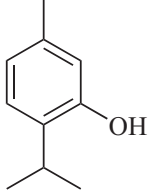
Simple oral and throat irritation can be treated with an antiinflammatory and antiseptic mouthwash, including the thymol type associated with a visit to the dentist. Many essential oils are used as oral antiseptics, deodorizers and antiinflammatory agents, including mint, clove, eucalyptus and lemon oils, as well as menthol and thymol. These can be incorporated into artificial saliva products, used for relieving dry mouth, which are composed of either animal mucins or hydroxymethoxycellulose derivatives.

THYMOL EU

Thymol (Fig. 24.1) was originally extracted from thyme (*Thymus* spp.) and is present in many oils, including ajowan, but is now more easily synthesized chemically. It is antiseptic, deodorizing and antiinflammatory and is widely used in dental products (e.g. compound thymol glycerin). Thymol causes irritation in high concentrations when applied externally, and should not be swallowed in significant amounts. Normal doses associated with the herb do not normally cause problems.

PEPPERMINT OIL, *MENTHA* × *PIPERITA* L. (MENTHAE PIPERITAE AETHEROLEUM) EU

Peppermint oil is antiseptic, deodorizing and antiinflammatory and is widely used in skin and dental products. Other species of mint, such as spearmint, are also used for the same purpose (for botanical and chemical details, see Chapter 14).



Thymol

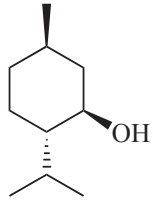
Fig. 24.1

Constituents

The major constituents are menthol (30–55%) and menthone (14–32%), with isomenthone (2–10%), menthofuran (1–9%), menthyl acetate (3–5%), 1,8-cineole (6–14%), limonene (1–5%), pulegone (not more than 4.0%) and carvone (not more than 1.0%). Menthol (Fig. 24.2) can cause irritation in high concentrations.

SAGE, *SALVIA OFFICINALIS* L. (SALVIAE FOLIUM) EU

The genus *Salvia* is one of the largest of the family Lamiaceae and many of its species, especially those rich in essential oil, have pharmaceutical uses. This common garden plant (garden sage) and culinary shrub has conspicuous blue flowers and relatively large leaves (3–5 cm long, 1–2.5 cm broad), which are oblong or lanceolate, rounded at the base and at the apex, and crenulate at the margin. The young leaves especially are covered with a white layer of fine hairs. The leaves have a characteristic uneven upper surface and prominent lower venation. The taste and odour are characteristic, pungent and aromatic. Sage is a popular culinary herb. *S. triloba* L.f. is also rich in essential oil and has similar topical uses as *S. officinalis* (see also Chapter 16, p. 232).



(–)-Menthol

Fig. 24.2

Constituents

The leaves are rich in essential oil with α- and β-thujone as the major components (normally about 50%), with cineole, borneol and others. It also contains rosmarinic acid. Diterpenes and flavonoids are two other important classes of natural products prominent in this species. There are differences in the composition of the essential oil depending on the origin of the plant material.

Therapeutic uses and available evidence

The use of sage leaf, in the form of a tea used as a gargle, is traditional for soothing inflammation of the mucous membranes of mouth and throat. Rosmarinic acid is well known for its antiviral and antiinflammatory effects, sage essential oil is antibacterial and antifungal, and an aqueous extract of sage leaf has been shown to have analgesic and antiinflammatory effects in rats, supporting this use of sage. In the doses used for mouthwashes it is generally considered to be safe. A throat spray containing echinacea and sage was recently compared to a chlorhexidine and lidocaine spray in a multicenter, randomized, double-blind, double-placebo controlled trial involving 154 patients with acute sore throats. They used two puffs every 2 hours, up to 10 times daily until they were symptom-free, for a maximum of 5 days. The main outcome measure was the comparison of response rates during the first 3 days, a response being defined as a decrease of at least 50% of the total symptoms compared to baseline. The echinacea/sage treatment showed similar efficacy to the chlorhexidine/lidocaine spray during the first 3 days, i.e. 63.8% in the echinacea/sage group and 57.8% in the chlorhexidine/lidocaine group. For all assessments of efficacy by the physician and patient, no difference between the two treatments was seen, and both were very well tolerated (Schapowal et al 2009).

CLOVE, *SYZYGIUM AROMATICUM* (L.) MERR. & L.M. PERRY (CARYOPHYLLI FLOS) EU

Cloves are obtained from the flower buds of *Syzygium aromaticum* (syn. *Eugenia caryophyllata* Thunb., Myrtaceae) which are collected prior to opening. The buds are brown, about 1–1.5 cm long, with a very characteristic shape, the lower portion consisting of the calyx tube enclosing in its upper half the immature flower. Taste and odour are highly

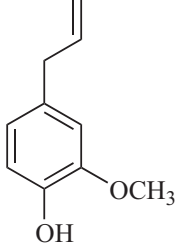
characteristic. On pressing a clove with the fingernail, oil should be exuded. Cloves are used as a culinary spice.

Constituents

The buds are very rich in essential oil (15–20%), consisting mainly of eugenol (Fig. 24.3), usually 85–90%, and numerous minor constituents, including acetyl eugenol, α- and β-caryophyllene, methyl salicylate. Tannins such as eugeniin, casuarictin, tellimagrandin I, and flavonoids, are found in the plant material but not in the oil.

Therapeutic uses and available evidence

Clove oil is used for the symptomatic relief of toothache and is a constituent of many dental preparations. The oil is useful in the treatment of inflammation of the mucous membranes of mouth and throat. It has antiseptic, antispasmodic, antihistaminic and anthelmintic properties, many of which are due to the eugenol content. Eugenol inhibits prostaglandin synthesis and the metabolism of arachidonic acid by human polymorphonuclear leukocytes, inhibits smooth muscle activity in vitro and is antiinflammatory (for review, see Chaieb et al 2007). Clove extracts are used in cosmetics and perfumery.



Eugenol

Fig. 24.3

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Schapowal, A., Berger, D., Klein, P., Suter, A., 2009. Echinacea/sage or chlorhexidine/lidocaine for treating acute sore throats: a randomized double-blind trial. Eur. J. Med. Res. 14, 406–412.

Miscellaneous supportive therapies for stress, ageing, cancer and debility

Although their effects are very difficult to evaluate, preventative medicines are extremely popular with patients and are an essential element of most types of Oriental medicine. They have been collected together here as they are generally used for a multitude of disorders, and to prevent degenerative conditions, including ageing and some forms of cancer. Most of the herbs mentioned here originated in Asia and China. In traditional Chinese medicine they are used to treat 'empty' diseases, to restore 'qi' energy and tonify the organs, having a balancing effect on yin and yang rather than affecting only one. They are thought to strengthen the immune system, improve memory and alertness, enhance sexual performance, promote healing and stimulate the appetite. In the West, the most important Chinese herbs are ginseng, ginkgo, astragalus, shizandra, reishi mushroom, baical scullcap and tea. In Ayurveda, some rejuvenating and tonic herbs are called 'rasayanas' and are considered to have a beneficial effect, balancing the tridosha. In Asian medicine, ashwagandha and *Centella asiatica* are very widely used. Many of these herbs contain saponins or steroidal compounds of some kind and it has been suggested that they act in a similar way to corticosteroids or enhance the effect of naturally occurring steroid hormones in the body. This type of drug is known as an adaptogen, and is considered to be a substance helping the body to deal with, or adapt to, stress or other adverse conditions.

While very contentious, this group is a fast growing area of phytotheray, but use is often based on very limited scientific evidence.

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CANCER CHEMOPREVENTION

During the 1960s and 1970s, work done at the University of Minnesota by LW Wattenberg showed that various compounds, especially from fruits and vegetables (indoles and isothiocyanates), could inhibit chemically induced tumours in laboratory animals. Termed 'chemoprophylaxis of carcinogenesis', this was of obvious benefit to maintenance of human health and had enormous dietary significance. After intensive studies using retinoids (vitamin A related natural products), the term 'cancer chemoprevention' was first used.

Cancer chemoprevention can be defined as 'the prevention of cancer in human populations by ingestion of chemical agents that prevent carcinogenesis'. It is also important to differentiate between cancer prevention (e.g. cessation of cigarette smoking) and cancer chemotherapy (the use of cytotoxic drugs after cancer diagnosis). Cancer chemoprevention has now developed into a well-defined discipline. Several recent epidemiological studies have demonstrated that dietary factors may reduce the incidence of cancers. In one study, involving 250,000 people, an inverse correlation was found between the incidence of lung cancer among people who smoke and consume carotene-rich foods. As well as carotenoids, there was a similar finding for vitamin C and oesophageal and stomach cancers; selenium and various cancers; and vitamin E and lung cancer. Epidemiological studies may help to find leads for chemopreventive agents, which can then be tested in laboratory experiments. Almost 600 'chemopreventive' agents are known and they are usually classified as: inhibitors of

carcinogen formation (ascorbic acid, tocopherols, phenols), inhibitors of initiation (phenols, flavones) and inhibitors of postinitiation events (β-carotene, retinoids, terpenes). Many are items of food or beverages (e.g. tea) and are sometimes called 'functional foods' or 'nutraceuticals'. Those that are used *purely* as foods are not covered here, but some others can be found in the chapters for which they are most useful (e.g. ginger, Chapter 14; garlic, Chapter 15). Further examples are given in Table 25.1.

Chemopreventive agents may even work in synergy, with several components contributing to the overall effect, which may be the case with plant drugs. This approach has great promise, with both natural products and synthetics being potentially useful. Dietary campaigns by government bodies, the American Cancer Society and others recommend that 5–7 servings of vegetables be consumed daily to function as a source of cancer chemopreventive agents. However, it is not reasonable to assume that chemopreventive agents will safeguard humans from known carcinogenic risks such as smoking. As knowledge of these agents increases they will play an increasing role in cancer prevention. Chemoprevention will not be covered further, apart from tea, as it is a vast subject in its own right. However, there are some useful recent reviews which discuss compounds, mechanisms and future directions available, such as Shu et al (2010), Gullett et al (2010) and Cerella et al (2010). Some data on the chemopreventive effects of garlic, anthocyanins (bilberry) and others can be found in the monographs of these plants.

Table 25.1 Known types of chemopreventive agents

GROUP	EXAMPLES
Micronutrients Food additives Antioxidants	Vitamins A, C and E, selenium, calcium, zinc
Non-nutritive molecules	Carotenoids, coumarins, indoles, alkaloids
Industrial reagents	Photographic developers, herbicides, UV-light protectors
Pharmaceuticals	Retinoids, antiprostaglandins, antithrombogenic agents, non-steroidal antiinflammatory drugs
Hormones and antihormones	Dehydroepiandrosterone, tamoxifen

TONICS, STIMULANTS, ADAPTOGENS AND SUPPORTIVE THERAPIES

AÇAI BERRY, *EUTERPE OLERACEA* MART. (EUTERPE FRUCTUS)

The fruits of the palm *Euterpe oleracea* Martius (açai, Arecaceae) have been acclaimed as having a wide range of health-promoting and therapeutic benefits due to their reportedly high levels of antioxidants. Açai has a history of use as a medicinal plant and as a staple food in many parts of Brazil. Traditionally, it has been used to treat fevers, skin complications, digestive disorders and parasitic infections. In recent years, açai berry has been advertised widely, for example, via the internet.

Constituents

Açai has a relatively high content of polyphenols. Most notable are anthocyanins and flavonoids, as well as fatty acids. Recently, small amounts of lignans have been reported.

Therapeutic uses and available evidence

This botanical drug has become very popular despite a lack of scientific evidence. Clinical data are lacking. The high content of polyphenols has been linked to a range of reported (mostly in vitro) antioxidant, antiinflammatory, antiproliferative and cardioprotective properties. Açai demonstrates promising potential with regard to antiproliferative activity and cardioprotection, but further studies are required (Heinrich et al In press).

ASHWAGANDHA, *WITHANIA SOMNIFERUM* (L.) DUNAL.

Ashwagandha, also known as winter cherry (Solanaceae), is a woody shrub native to the Middle East, Africa and parts of Asia, growing in stony and semi-arid regions; it is cultivated widely. The leaves are elliptical with an acute apex and the flowers campanulate and greenish yellow, developing into red berries enclosed in a papery membrane. The dried root is used medicinally. Ashwagandha has been used in Ayurvedic medicine for over 4000 years, as an adaptogen, sedative and tonic for debility. It is used to enhance fertility in both men and women, and as an aphrodisiac. The name 'ashwagandha' comes

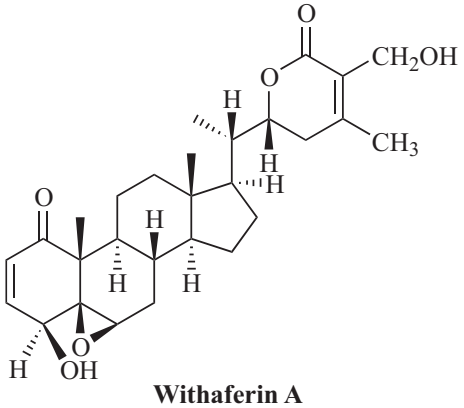
from the Sanskrit *ashva* (meaning 'horse') and *gandha* (meaning 'smell'), and refers to the odour of the root. It is also widely used for inflammation, colds, asthma and many other disorders.

Constituents

The root contains steroidal lactones (the withanolides A–Y), withaferin A (Fig. 25.1), withasomniferols A–C and others, phytosterols (such as the sitoindosides) and the alkaloids anahygrine, cuscohygrine, ashwagandhine, ashwagandhinine, withasomnine, withaninine, somniferine and others.

Therapeutic uses and available evidence

Extracts are antioxidant, immunomodulatory and sedative but, despite their wide usage, much of the clinical knowledge is still anecdotal. The few clinical trials which have been carried out are of doubtful quality and cannot be used to confirm efficacy, but they do show that the herb is generally safe. Many of the pharmacological effects have been substantiated in animal studies: for example, the adaptogenic and antistress activity was found to be comparable to that of ginseng, in mice and rats, and immunomodulatory activity has been confirmed. The extract has sedative activity and is reported to be anxiolytic, acting via the GABA-ergic system (Bhattarai et al 2010) and numerous other actions have been documented (for review, see Kulkarni and Dhir 2008). The usual dose of powdered root is 3–6 g daily. Side effects are rare but high doses can cause gastrointestinal irritation.



Withaferin A

Fig. 25.1

CENTELLA, *CENTELLA ASIATICA* (L.) URBAN (CENTELLAE HERBA)

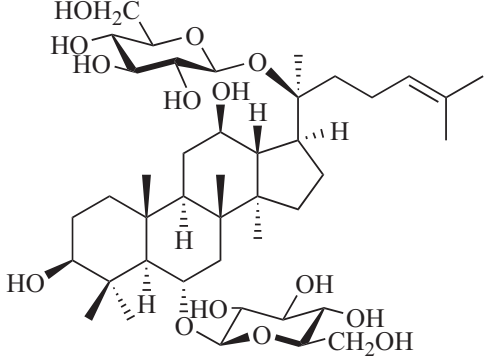
The herb has already been described in Chapter 22 (Skin). In addition to the wound healing effects, the plant is considered a 'rasayana' in Ayurvedic medicine; it enhances the immune system and is considered to have a rejuvenating, neurological 'tonic' and mild sedative effect. The immunomodulating effects of the herb have been shown in vitro and in vivo in mice. Studies in rats have shown that asiatic acid has some benefits on memory and learning (Nasir et al 2011), and that the extract can protect against certain types of neurodegeneration (Haleagrahara and Ponnusamy 2010), but in general, evidence for this use is lacking. A small double-blind, placebo-controlled, randomized trial in healthy elderly volunteers in Thailand found that their health-related quality of life was improved and lower extremity strength increased after taking centella extract for 3 months (Mato et al 2009). It may be taken orally, often as an infusion, and applied topically. Other reported effects for the herb include anti-ulcer activity and spasmolytic effects. The powdered leaf is taken at an internal dose of 0.5–1 g daily, or the equivalent in the form of an extract.

GINSENG, *PANAX GINSENG* C.A. MEYER *(PANAX RADIX)*, *ELEUTHEROCOCCUS SENTICOSUS* (RUPR. & MAXIM.) MAXIM. AND RELATED 'GINSENG' SPECIES

Ginseng root in commerce is obtained from *Panax ginseng* C. A. Meyer (Korean or Chinese ginseng, Araliaceae) and other species. American ginseng is from *P. quinquefolius* L., but Siberian ginseng comes from a different but related genus, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. *P. ginseng* is native to China but cultivated widely elsewhere. The root is spindle-shaped, ringed, and divided into two or three equal branches. Red Korean ginseng (from *P. ginseng*) is about 8 years old; it is matured and roasted, and is the most highly regarded form. Ginseng products are liable to adulteration and falsification (often with liquorice), as true ginseng is expensive.

Constituents

All types contain saponin glycosides (the ginsenosides Ra, Rb, Rg_1, Rg_2, Rs, etc.; Fig. 25.2). The ginsenosides are sometimes referred to as the panaxosides, but this nomenclature uses the suffixes A–F, which do not correspond to those of the ginsenosides.



Ginsenoside Rg_1

Fig. 25.2

In Siberian ginseng (*Eleutherococcus*), the saponins (eleutherosides A–F) are chemically different, but have similar properties. Glycans (panaxans) also occur in *P. ginseng*. The actual composition of ginseng extracts depends upon the species and method of preparation.

Therapeutic uses and available evidence

Ginseng is taken as a tonic for debility, insomnia, natural and premature ageing, to increase alertness and improve sexual inadequacy, and for diabetes, as well as an adaptogen to relieve stress and improve stamina and concentration. It has been suggested that these effects are due to changes in cholinergic activity and also neuro-protection, as well as antioxidant activity (Wang et al 2007). The adaptogenic effect may be due to the elevation of serum levels of corticosteroids and the reduction of catecholamines, which results in homoeostasis. Ginsenoside Rb_1 acts as a central nervous system sedative and Rg_1 has antifatigue and stimulant properties. In animals, an extract increases the capacity of skeletal muscle to oxidize free fatty acids in preference to glucose to produce cellular energy, which would support the antifatigue activity seen in conventional exhaustion tests. Ginseng also has a traditional use in diabetes, and the glycans (panaxans A–E) are hypoglycaemic in mice. Other documented effects include immunomodulatory activity, potentiation of analgesia and anticancer effects (by ginsenosides R_{s3} and R_{s4}).

Trials of ginseng for improving 'quality of life', including mental health parameters, show beneficial effects for up to 8 weeks of treatment, but as far as cognition is concerned, a recent Cochrane review concludes that further, better quality studies are needed (Geng et al 2010). Since that review, the results of a placebo-controlled, double-blind, randomized, crossover study assessing the effects of *Panax ginseng* on subjective mood and aspects of 'working' memory processes in healthy young adults, following both single dose and sub-chronic (7 days) ingestion, has been published. Dose-related treatment effects were found: 200 mg slowed a fall in mood, but also slowed responding on a mental arithmetic task across day 1, whereas the 400 mg dose also improved calmness (restricted to day 1) and improved mental arithmetic across days 1 and 8. No evidence of additional benefits, nor attenuation of acute effects, was found with repeated ingestion (Reay et al 2010). The dose is very variable but, in general, for a short course in the young and healthy, 0.5–1 g daily is recommended for up to 20 days; for long-term treatment in the sick or elderly, 0.4–0.8 g daily is more usual. Ginseng is taken widely, and side effects are well documented. They include oestrogenic effects, hypertension and irritability. A 'ginseng abuse' syndrome has been described.

LINGZHI OR REISHI MUSHROOM, *GANODERMA* SPP.

Ganoderma lucidum (Curtis Fr.) P. Karst., *G. japonicum* (Fr. Lloyd) and other species of mushroom (Polyporaceae) grow on tree stumps (mainly conifers) in China, Japan and North America. It is now cultivated for commerce. In China, the fungus is known as lingzhi, and in Japan, as reishi. The fruiting body takes several forms, including a rare, branched or 'antler' type, in addition to the more usual mushroom shape. The colour varies from red, through orange and brown, to black, with the red and antlered varieties being more highly prized. The cap is circular, kidney- or fan-shaped, leathery with a smooth or rippled upper surface, and an under surface that shows the spore tubes. Lingzhi is a very important Chinese medicine; it has been immortalized in Oriental paintings and was used frequently by Taoist monks.

Constituents

The mature fruiting body of the fungus contains a series of triterpenes, mainly lanostanes such as the ganoderic acids A–Z, ganoderals A and B, ganoderiols A and B, epoxyganoderiols A–C, ganolucidic acids A–E, lucidones A–C, lucidenic acids A–M.

Polysaccharides, mainly glucans and arabinoxyoglucans, and peptidoglycans (known as ganoderans A–C) are also present.

Therapeutic uses and available evidence

Lingzhi is used as an adaptogen and general tonic, in the hope of prolonging life, retarding ageing and generally improving wellbeing and mental faculties. The most common indication is to enhance the immune system, and various animal and clinical studies support such a use. More recently, reishi has been applied as an adjunctive treatment to chemotherapy and radiation in cancer patients, to support immune resistance. The active principles are considered to be the triterpenes and polysaccharides. Extracts inhibit angiotensin-converting enzyme and produce hypotensive effects; cholesterol-lowering effects have been seen in animals. It is also a sedative, liver protectant and cholesterol-lowering agent (for review, see Sanodiya et al 2009). Clinical studies to support the uses are few and some are of doubtful quality.

The dose of the dried fruiting body of the fungus is 6–12 g daily, or the equivalent in extract. Lingzhi is well tolerated, although transient side effects of gastrointestinal disturbance and rashes in sensitive individuals have been reported. Animal studies have shown no toxic effects after long-term high doses, but as with other immune modulators it should probably be avoided in auto-immune disease.

ROSENROOT, *RHODIOLA ROSEA* L. (RHODIOLAE ROSEAE RHIZOMA)

Also known as Golden root, Aaron's rod, *Rhodiola rosea* (Crassulaceae) grows in cold regions of the world, including much of the Arctic, mountainous regions of Central Asia and Europe, and the Rocky Mountains. It is a dioecious perennial reaching 5 to 35 cm in height.

Constituents

The main active constituents of the root and rhizome are monoterpene alcohols and their glycosides, such as salidroside (previously known as rhodioloside or rhodosin), rhodioniside, rhodiolin, rosin, rosavin, rosarin and rosiridin. These compounds are thought to be responsible for the adaptogenic properties of rhodiola. Other phenolic constituents such as p-tyrosol, gallic acid, caffeic acid, chlorogenic acid and flavonoids (catechins and proanthocyanidins) are present. Geraniol and other essential oil constituents, such as geranyl formate, geranyl acetate, benzyl alcohol and phenylethyl alcohol, give the root its rose-like odour.

Therapeutic uses and available evidence

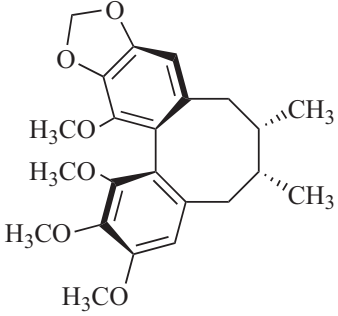
Rhodiola rhizome preparations exhibit adaptogenic effects, and these include neuroprotective, cardioprotective, anti-fatigue, antidepressive, anxiolytic and CNS stimulating activity. A number of small clinical trials demonstrate that repeated administration of a Rhodiola rosea extract (SHR-5) may exert an anti-fatigue effect and increase mental performance in healthy subjects (measured as an ability to concentrate), and reduce burnout in patients with mild fatigue syndrome. Rhodiola may help in mild to moderate depression and generalized anxiety. Mechanisms of action which may contribute to the clinical effect include interactions with the HPA-system (reducing cortisol levels) and defense mechanism proteins (some heat shock proteins). It does not seem to interact with other drugs and appears to be safe, with only minor adverse effects. For review, see Panossian et al 2010, Panossian and Wikman 2009.

SCHISANDRA, *SCHISANDRA CHINENSIS* (TURCZ.) BAILL. (SCHISANDRAE CHINENSIS FRUCTUS)

The magnolia vine (*Schisandra*, Schisandraceae,) is also known as gomishi in Japan, and Wu-wei-Zi in China. It is a monoecious liana, native to Northern China, Korea, Japan and eastern Russia, usually found climbing round tree trunks. The leaves are elliptical and the flowers cream with a pleasant odour. The fresh berries are scarlet, small and ovoid, hanging in clusters and are the main botanical drug used. When dry they are wrinkled, dark reddish brown, containing a sticky pulp and a yellow kidney-shaped seed. *Schisandra sphenanthera* Rehder & E. H. Wilson is also widely used for similar purposes.

Constituents

The active constituents are lignans, including schizandrin A (=deoxyschisandrin or wuweizu A), schizandrin B (=wuweizu B or γ-schizandrin B; Fig. 25.3), schizandrol A (=schizandrin), schizandrol B (=gomisin A), schisandrin C, schisantherin A (=gomisin C), schisantherin B (=gomisin B), gomisins H, K, L, M, N, schizanhenol, wuweizu C, schisantherin C and others.



Schisandrin B

Fig. 25.3

Therapeutic uses and available evidence

Schisandra has been used in China since ancient times to prolong life and increase energy ('qi') and act as a general and sexual tonic, especially for men. It is also used to reduce sweating, detoxify the liver, enhance kidney function and suppress cough in lung disease. The adaptogenic and antifatigue properties have been tested in several animal studies; for example, the effect on the physical recovery of racehorses was found to be beneficial, as well as producing a general improvement in performance. Schizanhenol and schizandrin B protect against peroxidative damage associated with ageing and ischaemia in the rat brain, and a human study has suggested that intellectual activity can be enhanced. Many pharmacological studies support the use of schisandra, although few good clinical trials have been performed. Hepatoprotective effects have been documented in animal and cell culture studies. Schizandrin B, schisandrin C and gomisin A reduced liver enzyme levels and prevented histological damage in experimental models of liver injury, inhibited lipid peroxidation and stimulated glycogen synthesis in the liver. Antioxidant and free radical scavenging effects have also been described in vivo and in vitro. Deoxyschisandrin, gomisin A, B and C increase liver cytochrome P450 enzymes, which supports the detoxifying and anticancer properties attributed to the plant. Antitumour-promoting and antiinflammatory properties have also been shown in skin and the lignans are known to be platelet activating factor antagonists. For review, see Panossian and Wikman (2008, 2009). Daily doses of powdered berry are usually 1.5–6 g or higher if used to treat kidney disease.

Few toxicity studies have been carried out but, although relatively safe, schisandra is reputed to increase gastric acidity and may cause allergy in susceptible individuals. It should be avoided during pregnancy (possible uterine stimulation) and epilepsy.

Skullcap, *Scutellaria baicalensis* Georgi (Scutellaria baicalensis radix)

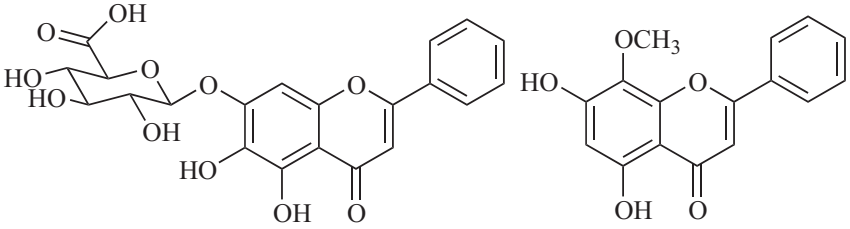
Scutellaria baicalensis (Huan qin, Lamiaceae) is sometimes known as baical skullcap to differentiate it from American skullcap (*S. laterifolia* L.). It grows in northern China, Siberia and Manchuria. The leaves are opposite, lanceolate and sessile with an acute apex. The flowers are blue, with a helmet-shaped upper lip (hence the name). The root is used medicinally.

Constituents

The root contains flavonoids including baicalin, baicalein, wogonin, chrysin, oroxylin A, skullcapflavones I and II, and others (Fig. 25.4).

Therapeutic uses and available evidence

Skullcap is used for a wide variety of ailments, particularly fevers, infections, jaundice, thirst and nosebleeds, and as an antidote and sedative. Baicalin is antiinflammatory and anti-allergic; it inhibits the formation of lipoxygenase products and, to a lesser extent, cyclo-oxygenase products in leukocytes. It also inhibits the generation of inflammatory cytokines and is synergistic with β-lactam antibiotics against methicillin-resistant *Staphylococcus aureus* in vitro. Extracts of *S. baicalensis* inhibit lipid



Baicalin **Wogonin**

Fig. 25.4

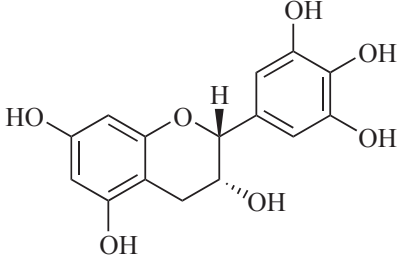
peroxidation in rat liver and the herb has been clinically tested in China in patients with chronic hepatitis, where it improved symptoms in over 70% of patients, increasing appetite, relieving abdominal distension and improving the results of liver function tests. Wogonin also suppresses production of hepatitis B virus surface antigen. The flavones interact with the benzodiazepine-binding site of the $GABA_A$ receptor, with wogonin and baicalein being the most potent; this supports the sedative use of the herb. Baicalein is antigenotoxic in vitro and inhibits adhesion molecule expression induced by thrombin and cell proliferation of several types of cells. Wogonin inhibits nitric oxide production in activated C6 rat glial cells, acting via NF-κB inhibition and thus suppressing cell death. It also reduces skin inflammation in mice (induced by phorbol ester expression of COX-2) and inhibits monocyte chemotactic protein-1 gene expression in human endothelial cells. Antioxidant and antibiotic activities have also been reported for extracts. These activities all support the antiinflammatory and other uses of skullcap, although clinical trial evidence is sparse (for review, see Li-Weber 2009, Wang et al 2007). The daily dose of skullcap root is usually 5–8 g. Generally, baical skullcap is well tolerated, but little information as to side effects and contraindications is available.

TEA, *CAMELLIA SINENSIS* (L.) KUNTZE (GREEN TEA LEAVES: THEAE VIRIDIS FOLIUM; BLACK TEA LEAVES: THEAE NIGRAE FOLIUM)

Tea (*Camellia sinensis*, Theaceae) is cultivated in China, India, Sri Lanka, Kenya, Indonesia and elsewhere. Green tea is produced in China and Japan; it is not processed and thus differs from black tea, which is fermented and produced in India, Sri Lanka and Kenya. Oolong tea is partially fermented. The leaf buds and very young leaves are used to prepare the beverage and extracts for medicinal use.

Constituents

Tea contains caffeine, and much smaller amounts of other xanthines such as theophylline and theobromine. The polyphenols are the antioxidant constituents [in green tea these are mainly (−)-epigallocatechin; Fig. 25.5], together with theogallin, trigalloyl glucose. In black tea, they have been oxidized to form the 'tea pigments', the theaflavins, thearubigens and theaflavic acids.



(–)-Epigallocatechin

Fig. 25.5

Therapeutic uses and available evidence

Tea is a stimulant, diuretic, astringent and antioxidant. Green tea is used medicinally more frequently than black tea. The stimulant and diuretic properties are due to the caffeine content, and the astringency and antioxidant effects to the polyphenols (Wang et al 2007).

Tea is useful in diarrhoea, and in China is used for many types of dysentery. The polyphenols in green tea have cancer chemopreventive properties due to their antioxidant capacity. Habitual consumption of green tea is generally associated with a lower incidence of cancer (for review, see Lambert and Elias 2010) and black tea is now known to have similar health benefits, which are ascribed to the tea pigments (for review, see Kumar et al 2010). Anti-inflammatory and antitumour effects have been described, and attributed to inhibition of the transcription factor NF-κB, and the risk of breast and stomach cancers appears to be lower for green tea drinkers. Black tea consumption is associated with a lower risk of death from ischaemic heart disease and has been shown to reverse endothelial dysfunction in coronary heart disease. Tea is also antimicrobial and anticariogenic, and is even reputed to help weight loss. Tea is drunk in nearly every country in the world for its refreshing, mildly stimulating and analgesic effects. There is no recommended dose for tea, and consumption varies widely.

Tea as a beverage is non-toxic in the usual amounts ingested, although it can cause gastrointestinal upsets and nervous irritability, due to the caffeine content. However there is now some concern about the safety of concentrated preparations or excessive consumption of green tea. Cases of hepatotoxicity have been associated with consumption of high doses of green tea-containing dietary supplements (10–29 mg/kg/d p.o.). In most cases, patients presented with

elevated serum alanine aminotransferase (ALT) and bilirubin levels and in some cases liver biopsies were performed, and periportal and portal inflammation were observed. All cases resolved following cessation of supplement consumption, and re-injury was observed in some studies when the subject began reusing the same preparations, suggesting a causative effect of the green tea. There is also a case report of a 45-year-old man who developed jaundice and elevated serum ALT following consumption of 6 cups/d green tea infusion for 4 months (reviewed by Mazzanti et al 2009).

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